

Triglyceride and Triglyceride-like Prodrugs of Glycogen
Phosphorylase Inhibiting Compounds

Cross-Reference to Related Application

5 This application claims the benefit of U.S.
Provisional Application No. 60/426,465, filed
November 14, 2002 which is incorporated herein by
reference in its entirety

10

Field of the Invention

The present invention relates to prodrugs capable of
selectively targeting the absorption, processing and
delivery of glycogen phosphorylase inhibiting compounds
15 to the liver. Further, the present invention relates to
methods for using such prodrug compounds and to
pharmaceutical compositions containing such prodrug
compounds.

20

Background of the Invention

Approximately 100 million people worldwide suffer
from type II diabetes, which is typically characterized
by hyperglycemia due to excessive hepatic glucose
production and peripheral insulin resistance, the root
25 causes for which are as yet unknown. Hyperglycemia is
considered to be the major risk factor for the
development of diabetic complications, such as
retinopathy, neuropathy, nephropathy and macrovascular
disease.

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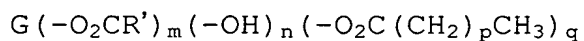
Accordingly, hepatic glucose production is an
important potential target for type II diabetes therapy.
The liver produces glucose by glycogenolysis (breakdown
of the glucose polymer glycogen) and gluconeogenesis
(synthesis of glucose from 2- and 3- carbon precursors).
35 Particularly, glycogenolysis is catalyzed in the liver,

muscle and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase. Prior studies suggest that glycogenolysis may make an important contribution to hepatic glucose output in type II diabetes. See WO 96/39384; WO 96/39385; EP 978279; Proc. Natl. Acad. Sci. USA 1998, 95, 1776-1781; J. Med. Chem. 1998, 41, 2934-2938. Thus, glycogen phosphorylase inhibitors are believed to be a useful therapeutic agent for treating type II diabetes and delaying the onset of diabetic complications by decreasing hepatic glucose production and lowering glycemia, while providing minimal risk of hypoglycemia and weight gain. See *Id.*

However, inhibition of glycogen phosphorylase in tissues outside of the liver may be undesirable, for instance by limiting muscle contraction in healthy muscle tissue. Therefore, for the purpose of treating type II diabetes, it may be desirable to restrict glycogen phosphorylase inhibition to the liver, and prodrug compounds with the ability to selectively deliver glycogen phosphorylase inhibiting compounds to the liver would provide a significant advantage over the prior art.

Summary of the Invention

In accordance with the present invention, prodrugs of a glycogen phosphorylase inhibiting compounds are provided, said prodrug compounds having the formula I



30

I

wherein G is a C₃ to C₅ branched or straight carbon chain and (-O₂CR'), (-OH) and (-O₂C(CH₂)_pCH₃) are attached to any available carbon atom along G;

35 m is an integer from 1 to 4;

 n is an integer from 0 to 3;

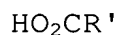
p is an integer from 0 to 16;

q an integer from 0 to 3;

where the sum of m, n and q is 3 or 4; and

R' and -O₂CR' can be defined as fragments of

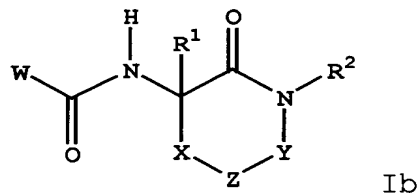
5 compounds of formula Ia :



Ia

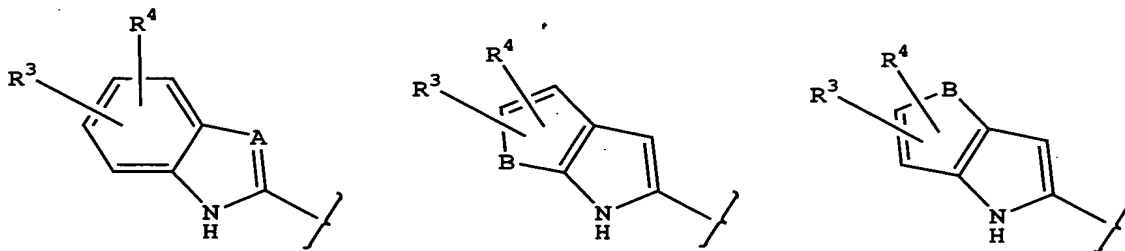
where "HO₂C" represents a carboxyl group located
upon any available position within R', and R' is as
10 defined below. In the compounds of formula I, -O₂CR' is
linked to G as an ester of this carboxyl group.

Compounds of formula Ia are further defined in
relation to compounds of formula Ib:



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W is a bicyclic hetroaryl of the structure

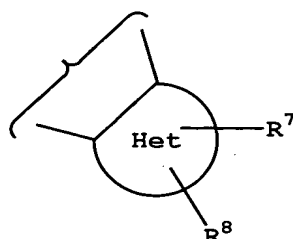
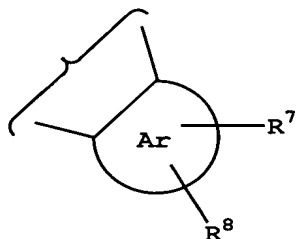


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X is -O-, -S-, -SO₂-, -CHR⁵-, -CHR⁵O-, -CHR⁵S-,
-CHR⁵SO₂-, -CHR⁵CO- or -CH₂CHR⁵-;

Y is a bond or -CHR⁶-;

25 Z is an aryl or heteroaryl group of the following
structure:



A is -CH- or -N-;

B is -O- or -S-;

5 R¹ is hydrogen, alkyl, aryl or alkenyl;

R² is hydrogen, alkyl, aryl, arylalkyl, heteroarylalkyl or alkenyl;

R³ and R⁴ are each independently hydrogen, halo, trifluoromethyl, cyano, alkyl or alkoxy;

10 R⁵ and R⁶ are each independently hydrogen, alkyl, aryl, alkenyl, CN, CN₄R^{9A} (tetrazole), CO₂R^{9A}, CONR^{9A}R^{9B} or CONR^{9A}OR^{9B};

R⁷ and R⁸ are each independently hydrogen, halo, trifluoromethyl, cyano, hydroxy, a hydrogen bonding group, alkyl, alkoxy, aryl, arylalkyl, heteroarylalkyl, 15 aryloxy or alkenyl; and

R^{9A} and R^{9B} are independently hydrogen, alkyl, arylalkyl, heteroarylalkyl or aryl, or R^{9A} and R^{9B} may optionally be cyclized together to form a ring, wherein 20 said ring may further be substituted with one to three additional hydrogen bonding groups;

wherein when R¹, R², R⁵, R⁶, R⁷ and R⁸ are alkyl, aryl, alkenyl, arylalkyl, heteroarylalkyl, alkoxy or aryloxy, R¹, R², R⁵, R⁶, R⁷ and R⁸ may each independently 25 be substituted with 1 to 3 hydrogen bonding groups.

Compounds of formula Ia represent the subset of compounds of formula Ib wherein R⁵ or R⁶ are CO₂H, or wherein one or more of R¹, R², R⁵, R⁶, R⁷ and R⁸ is alkyl, aryl, alkenyl, arylalkyl, heteroarylalkyl, alkoxy or 30 aryloxy, and at least one of R¹, R², R⁵, R⁶, R⁷ and R⁸ is

substituted with or contains a CO₂H hydrogen bonding group. Thus, R' represents the fragment of carboxyl containing compounds of formula Ib that is linked to G as an ester of the carboxyl group illustrated in formula Ia.

5 Preferred are compounds of formula I where (-O₂CR') represents a fragment of compounds of formula Ib wherein R⁵ or R⁶ is CO₂-, or wherein one or more of R¹, R², R⁵, R⁶, R⁷ and R⁸ is alkyl, aryl, alkenyl, arylalkyl, heteroarylalkyl, alkoxy or aryloxy, and one of R¹, R², R⁵,
10 R⁶, R⁷ and R⁸ is substituted with or contains a fragment of structure CO₂-.

The compounds of formula I are triglyceride and triglyceride-like prodrugs of the glycogen phosphorylase inhibiting compounds of formula Ia. Preferably, when the
15 prodrug compounds of formula I are absorbed by the liver, they will be converted within the liver into active agents, e.g., compounds of formula Ia. In this way, compounds of formula Ia may be selectively delivered to the liver thereby minimizing undesired concentrations of
20 compounds of formula Ia in the general circulation. Consequently, the compounds of the present invention may be used in the treatment of multiple diseases or disorders associated with glycogen phosphorylase activity in the liver, such as the treatment of diabetes, the
25 micro- and macrovascular complications associated with diabetes, such as retinopathy, neuropathy, nephropathy, as well as hyperglycemia, hypertension, hypertriglyceridemia, dislipidemia, Syndrome X, obesity, hyperinsulinemia, diabetic complications,
30 atherosclerosis, cardiovascular disease, delayed wound healing and other diseases.

The compounds of formula I further include all pharmaceutically acceptable salts and stereoisomers of formula I.

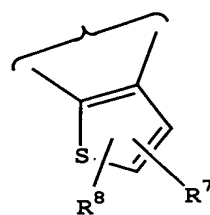
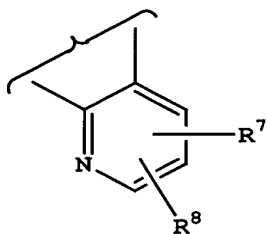
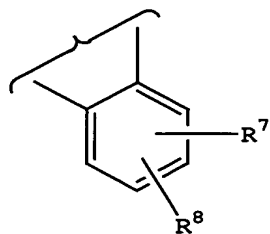
The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds. In particular, the present invention provides a
5 pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I, alone or in combination with a pharmaceutically acceptable carrier.

Further, in accordance with the present invention, a method is provided for preventing, inhibiting or treating
10 the progression or onset of diseases or disorders associated with the activity of the enzyme glycogen phosphorylase, such as defined above and hereinafter, wherein a therapeutically effective amount of a compound of formula I is administered to a mammalian, i.e., human,
15 patient in need of treatment.

The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

Further, the present invention provides a method for preventing, inhibiting or treating the diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of formula I and another compound of formula I and/or at
20 least one other type of therapeutic agent, is administered to a mammalian, i.e., human patient in need of treatment.
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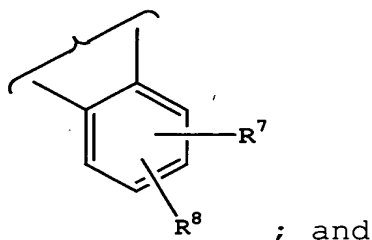
Preferred are compounds of formula I wherein Z is an aryl or heteroaryl group of the structure
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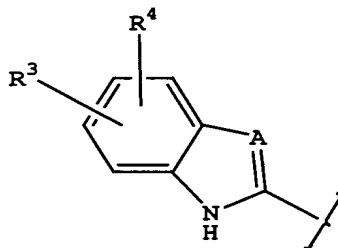
- The hydrogen bonding group substituent is preferably selected from the group consisting of OR^{9A} , OCO_2R^{10} , $CONR^{9A}R^{9B}$, CN , NO_2 , CN_4R^{9A} (tetrazole), $COCF_3$, COR^{9A} , CO_2R^{9A} , $CONR^{9A}R^{9B}$, $CONR^{9A}OR^{9B}$, $C(NR^{9A})NR^{9B}R^{9C}$,
 5 $CONR^{9A}SO_2R^{9B}$, SOR^{10} , SO_2R^{10} , SO_3H , $SO_2NR^{9A}R^{9B}$, $SO_2NR^{9A}COR^{9B}$, $SO_2NR^{9A}CONR^{9B}R^{9C}$, $POR^{9A}R^{9B}$, $PO_2R^{9A}R^{9B}$, $PO_3R^{9A}R^{9B}$, $PO_2R^{9A}NR^{9B}R^{9C}$, $NR^{9A}R^{9B}$, $NR^{9A}COR^{9B}$, $NR^{9A}C(NR^{9B})R^{9C}$, $NR^{9A}CO_2R^{9B}$, $NR^{9A}CONR^{9B}R^{9C}$, $NR^{9A}C(NR^{9B})NR^{9C}R^{9D}$, $NR^{9A}SO_2R^{9B}$, $NR^{9A}CONR^{9B}SO_2R^{9C}$, $NR^{9A}SO_2NR^{9B}R^{9C}$, $NR^{9A}POR^{9B}R^{9C}$, $NR^{9A}PO_2R^{9B}R^{9C}$, $NR^{9A}PO_3R^{9B}R^{9C}$ and $NR^{9A}PO_2R^{9B}NR^{9C}R^{9D}$;
 10 wherein
 R^{9C} and R^{9D} are each independently hydrogen, alkyl, arylalkyl, heteroarylalkyl or aryl; and
 R^{10} is independently alkyl, arylalkyl, heteroarylalkyl, or aryl;
 15 wherein R^{9A} , R^{9B} , R^{9C} , R^{9D} or R^{10} may further be substituted with one to three additional hydrogen bonding groups; and wherein two of R^{9A} , R^{9B} , R^{9C} or R^{9D} within the same hydrogen bonding group may optionally be cyclized together to form a ring, wherein said ring may further be
 20 substituted with one to three additional hydrogen bonding groups.

Further preferred embodiments include compounds of formula I wherein

- 25 R^1 is hydrogen;
 Z is

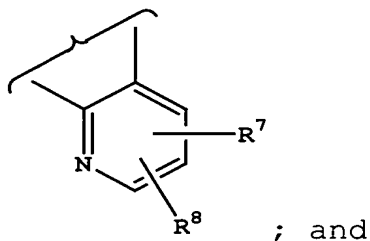


W is

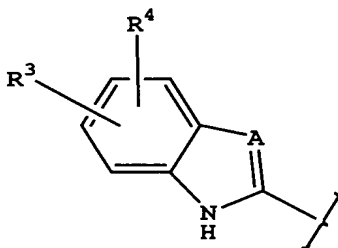


Additional embodiments include compounds of formula I wherein

- 5 R^1 is hydrogen;
 Z is



- 10 W is



More preferably, W is 5-chloroindol-2-yl.

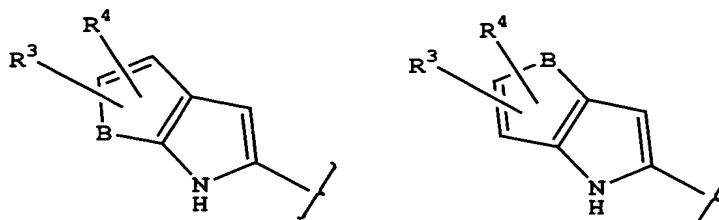
- 15 Further preferred embodiments include compounds of formula I, where $(-O_2CR')$ represents a fragment of compounds of formula Ib wherein

X is $-CHR^5-$, $-CHR^5O-$, $-CHR^5S-$, $-CHR^5SO_2-$, $-CHR^5CO-$ or $-CH_2CHR^5-$;

Y is $-CHR^6-$; and

- 20 R^5 or R^6 is CO_2- .

For compounds of formula I where W is



preferred are compounds of formula I wherein n is 0.

5 Detailed Description of the Invention

The following abbreviations have the indicated meanings:

- min = minute(s)
- 10 h or hr = hour(s)
- L = liter
- mL = milliliter
- μL = microliter
- g = gram(s)
- 15 mg = milligram(s)
- mol = moles
- M = molar
- mmol = millimole(s)
- HPLC = high performance liquid chromatography
- 20 HPLC/MS or LC/MS = high performance liquid chromatography/mass spectrometry
- MS or Mass Spec = mass spectrometry
- [M+H] = parent plus a proton
- [M-H] = parent minus a proton

25

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

- 30 The term "hydrogen bonding group(s)" describes functional groups that may form a hydrogen bond by either donating or accepting a hydrogen atom. Examples of suitable "hydrogen bonding group(s)" include, but are not limited to OR^{9A} , OCO_2R^{10} , $CONR^{9A}R^{9B}$, CN , NO_2 , CN_4R^{9A}

(tetrazole), COCF_3 , COR^{9A} , CO_2R^{9A} , $\text{CONR}^{9A}\text{R}^{9B}$, $\text{CONR}^{9A}\text{OR}^{9B}$,
 $\text{C}(\text{NR}^{9A})\text{NR}^{9B}\text{R}^{9C}$, $\text{CONR}^{9A}\text{SO}_2\text{R}^{9B}$, SOR^{10} , SO_2R^{10} , SO_3H , $\text{SO}_2\text{NR}^{9A}\text{R}^{9B}$,
 $\text{SO}_2\text{NR}^{9A}\text{COR}^{9B}$, $\text{SO}_2\text{NR}^{9A}\text{CONR}^{9B}\text{R}^{9C}$, $\text{POR}^{9A}\text{R}^{9B}$, $\text{PO}_2\text{R}^{9A}\text{R}^{9B}$, $\text{PO}_3\text{R}^{9A}\text{R}^{9B}$,
 $\text{PO}_2\text{R}^{9A}\text{NR}^{9B}\text{R}^{9C}$, $\text{NR}^{9A}\text{R}^{9B}$, $\text{NR}^{9A}\text{COR}^{9B}$, $\text{NR}^{9A}\text{C}(\text{NR}^{9B})\text{R}^{9C}$, $\text{NR}^{9A}\text{CO}_2\text{R}^{9B}$,
5 $\text{NR}^{9A}\text{CONR}^{9B}\text{R}^{9C}$, $\text{NR}^{9A}\text{C}(\text{NR}^{9B})\text{NR}^{9C}\text{R}^{9D}$, $\text{NR}^{9A}\text{SO}_2\text{R}^{9B}$, $\text{NR}^{9A}\text{CONR}^{9B}\text{SO}_2\text{R}^{9C}$,
 $\text{NR}^{9A}\text{SO}_2\text{NR}^{9B}\text{R}^{9C}$, $\text{NR}^{9A}\text{POR}^{9B}\text{R}^{9C}$, $\text{NR}^{9A}\text{PO}_2\text{R}^{9B}\text{R}^{9C}$, $\text{NR}^{9A}\text{PO}_3\text{R}^{9B}\text{R}^{9C}$,
 $\text{NR}^{9A}\text{PO}_2\text{R}^{9B}\text{NR}^{9C}\text{R}^{9D}$, and the like, wherein

R^{9A} , R^{9B} , R^{9C} and R^{9D} for each occurrence are each
independently hydrogen, alkyl, arylalkyl, heteroarylalkyl
10 or aryl; and

R^{10} is independently alkyl, arylalkyl,
heteroarylalkyl, or aryl.

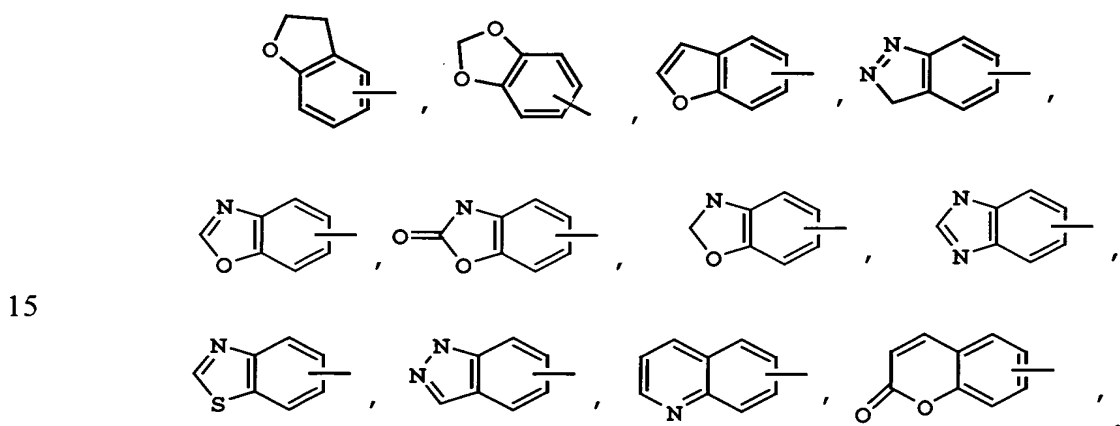
Moreover, R^{9A-9D} and R^{10} may be further substituted by
one to three hydrogen bonding groups, for example,
15 $\text{CONR}^{9A}\text{R}^{9B}$ may represent $\text{CON}(\text{Me})\text{CH}_2\text{CH}_2\text{OH}$. Optionally, two
of R^{9A} , R^{9B} , R^{9C} or R^{9D} within the same hydrogen bonding
group may be cyclized together to form a ring, for
example, $\text{CONR}^{9A}\text{R}^{9B}$ may represent $\text{CON}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2)$. Said
ring may further be substituted with one to three
20 additional hydrogen bonding groups, for example N-
acylated hydroxyproline or N-acylated 3,4-
dihydroxypyrrolidine.

The term "alkyl" as employed herein, alone or as
part of another group, includes straight chain, branched
25 chain and saturated cyclic hydrocarbons, containing 1 to
20 carbons, preferably 1 to 10 carbons, more preferably 1
to 8 carbons, in the normal chain, such as methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl,
hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl,
30 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl,
cyclopropyl, cyclohexyl, and the like.

Unless otherwise indicated, the term "alkenyl" as
used herein by itself or as part of another group refers
to straight or branched chain radicals of 2 to 20
35 carbons, preferably 2 to 12 carbons, and more preferably
2 to 8 carbons in the normal chain, that include one or
more double bonds in the normal chain, such as vinyl, 2-

propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl.

Unless otherwise indicated, the term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one additional fused heterocyclic ring, for example:



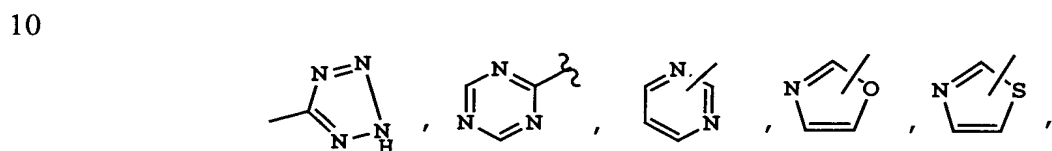
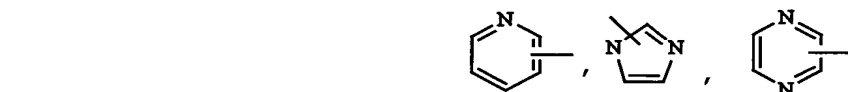
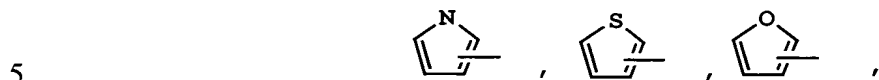
The term "arylalkyl" as used alone or as part of another group refers to an alkyl as defined herein, having an aryl substituent. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, phenethyl, benzhydryl and naphthylmethyl and the like.

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine and iodine.

Unless otherwise indicated, the term "alkoxy" or "aryloxy" as employed herein alone or as part of another group refers to an alkyl or aryl group, as defined herein, linked to an oxygen atom.

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or

4 hetero atoms such as nitrogen, oxygen or sulfur, and includes possible N-oxides. Examples of heteroaryl groups include the following:



15 and the like.

As used herein, the term "heteroarylalkyl" means an alkyl group having a heteroaryl substituent.

20 The term "cyano" as used herein, refers to a -CN group.

An administration of a therapeutic agent of the invention includes administration of a therapeutically effective amount of the agent of the invention. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat or prevent a condition treatable by administration of a composition of the invention. That amount is the amount sufficient to exhibit a detectable therapeutic or preventative or ameliorative effect. The effect may include, for example, treatment or prevention of the conditions listed herein. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent

of the condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance.

The compounds of formula I can be present as salts, which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C₁-C₄) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or p-toluene- sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tertbutyl, diethyl,

diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are
5 unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of formula I or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I which
10 contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate.

Preferred salts of the compounds of formula I which contain an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic
15 amines.

Any compound that can be converted in vivo to provide a bioactive agent may be considered a prodrug. Various forms of prodrugs are well known in the art and are described in:

- 20 a.) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch 31, (Academic Press, 1996);
- b.) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985); and
- c.) *A Textbook of Drug Design and Development*, P.
25 Krogsgaard-Larson and H. Bundgaard, eds. Ch 5, pgs 113 - 191 (Harwood Academic Publishers, 1991).

As known in the art, the term "prodrug esters" includes esters formed by reacting one or more hydroxyls
30 of a drug with simple acylating agents to generate acetates, pivalates, benzoates and the like. Alternatively, the term "prodrug esters" includes esters formed by reacting one or more carboxyl groups of a drug with simple alcohols to generate methyl, ethyl, and other
35 simple esters.

The concept of prodrugs that are well known in the art typically does not encompass triglyceride and triglyceride-like prodrugs such as those of formula I, both in terms of complexity and purpose. Although
5 triglyceride and triglyceride-like prodrugs are technically esters, they are much more complex than standard prodrug esters, which typically contain only one drug molecule made into a prodrug by derivatization of its carboxylic acid(s) as simple ester(s). Furthermore,
10 whereas standard prodrugs are typically used to overcome problems of solubility, absorption, or metabolism, the triglyceride and triglyceride-like prodrugs of formula I offer the possibility of liver selective activity.

All stereoisomers of the compounds of the instant
15 invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of formula I can exist in
20 enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional
25 methods for example, chromatographic or fractional crystallization.

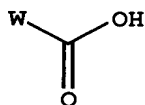
The compounds of formula I of the invention can be prepared as shown below in the following reaction schemes and description thereof, as well by using as relevant
30 published literature procedures that may be used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

Compounds of formula I may be prepared from the
35 compounds of formula Ia, $G(OH)_{m+n+q}$ or hydroxyl protected forms of $G(OH)_{m+n+q}$, and carboxylic acids $CH_3(CH_2)_pCO_2H$ or their acid chlorides by the methods described in

Bebernitz, et al., J. Med. Chem. 2001, 44, 512-523 and by using standard protecting group manipulations as described in Protective Groups in Organic Synthesis (2nd Edition, T.W. Greene and P.G.M. Wuts, John Wiley & Sons, 1991) and standard ester bond forming methods as described in Compendium of Organic Synthetic Methods (John Wiley & Sons). $G(OH)_{m+n+q}$, hydroxyl protected forms of $G(OH)_{m+n+q}$, carboxylic acids $CH_3(CH_2)_pCO_2H$ and their acid chlorides are commercially available or known in the art.

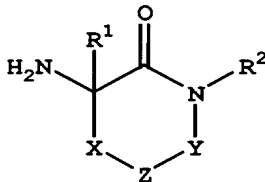
Compounds of formula Ia represent compounds of formula Ib, wherein R^5 or R^6 are CO_2H , or wherein one or more of R^1 , R^2 , R^5 , R^6 , R^7 and R^8 is alkyl, aryl, alkenyl, arylalkyl, heteroarylalkyl, alkoxy or aryloxy, and at least one of R^1 , R^2 , R^5 , R^6 , R^7 and R^8 is substituted with or contains a CO_2H hydrogen bonding group.

Compounds of formula Ib may be prepared by coupling carboxylic acids of formula II with amines of formula III using standard methods for amide bond formation, as known to those skilled in the art, for example, by treating equimolar amounts of compounds II and III in N,N-dimethylformamide solution at room temperature with equimolar amounts of 1-hydroxy-7-azabenzotriazole and 1-[3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.



II

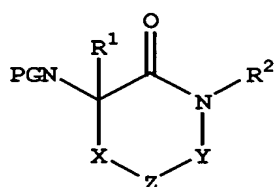
30



III

Carboxylic acids II may be prepared according to the routes and procedures described in WO 9639384, WO 9926659, and EP 1088824.

Amines III may be prepared by deprotection of the
 5 corresponding protected amines IV, in which the amino group is protected (PGN) as a carbamate, amide, phthalimide, N-benzyl derivative, or other standard amine protecting group, such as described in Protective Groups in Organic Synthesis (2nd Edition, T.W. Greene and P.G.M. Wuts, John Wiley & Sons, 1991).



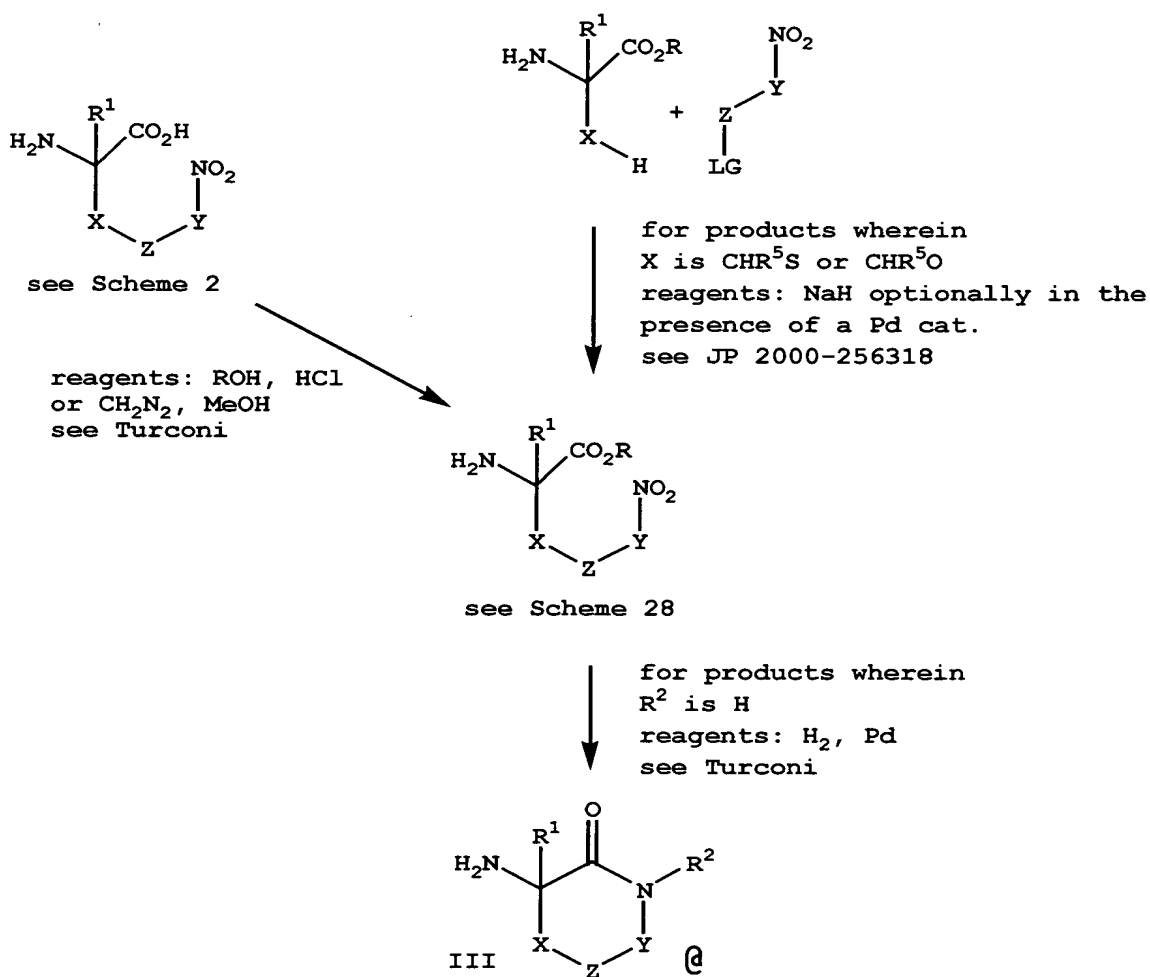
IV

Also included in the definition of protected amine
 15 IV are compounds in which the amino group is masked (PGN), i.e., the latent amino group may not fall into the strict definition of a protecting group, such as an azido or nitro group. Protected amines IV where the amino
 20 group is masked as a carbamate, amide, phthalimide, N-benzyl derivative, or other standard amine protecting group may be prepared from the amines III as described in Protective Groups in Organic Synthesis. Azido, nitro, and some protected amino groups, such as benzylamino, may
 25 be introduced by other means, such as displacement (azido and benzylamino). Carbamates may be prepared not only from the corresponding amine, but also from carboxylic acids by Curtius rearrangement, via the acid chloride, acyl azide and isocyanate (see Comprehensive Organic
 30 Synthesis, Editor B. M. Trost, Pergamon Press, 1991).

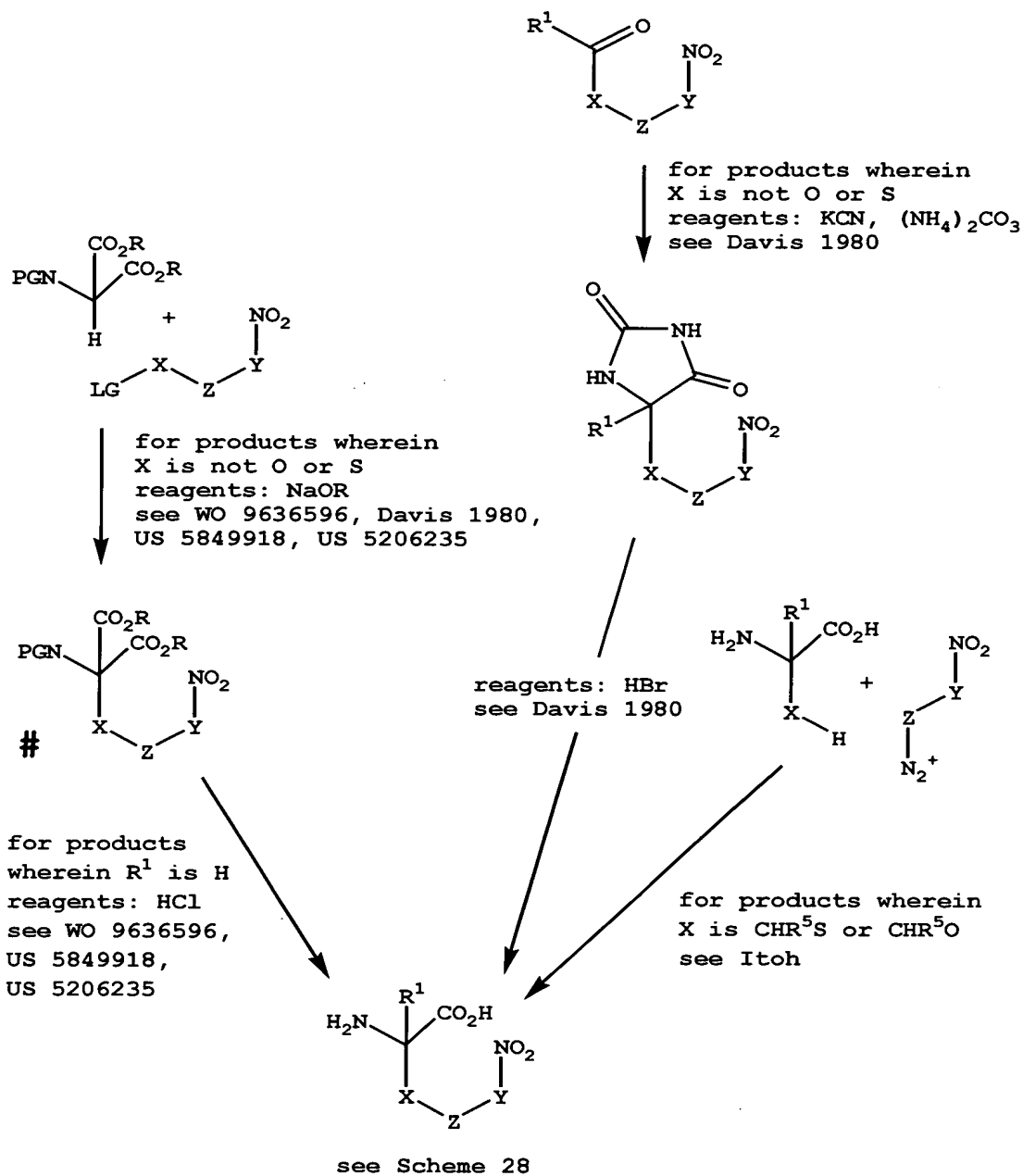
Synthetic schemes 1 to 28 provide general synthetic routes for the syntheses of amines III and protected amines IV. The reaction steps are subject to the constraints noted. For example, a reaction step noted

"for products wherein X is O or S" is subject to the constraint that only products in which X is O or S may be prepared.

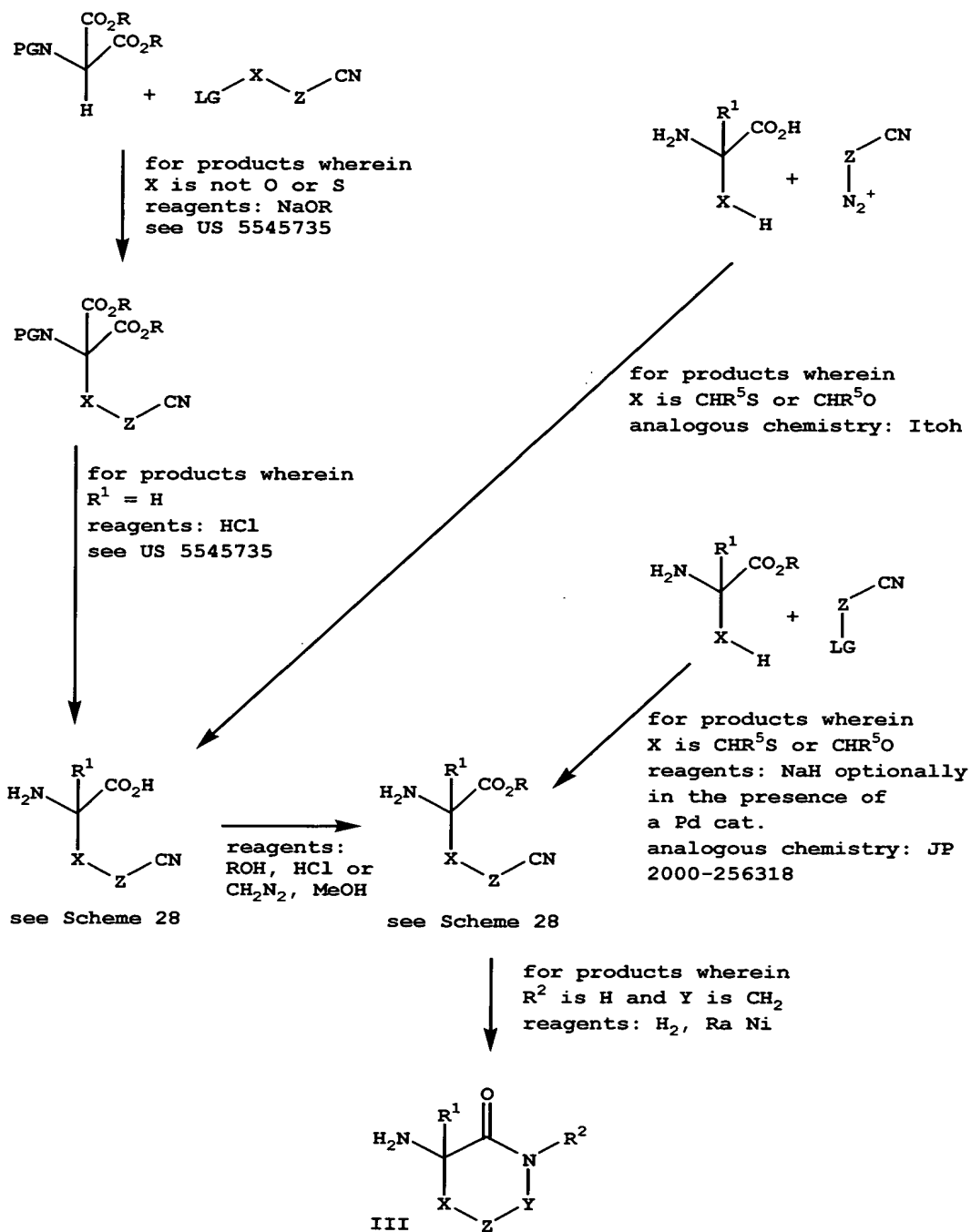
SCHEME 1



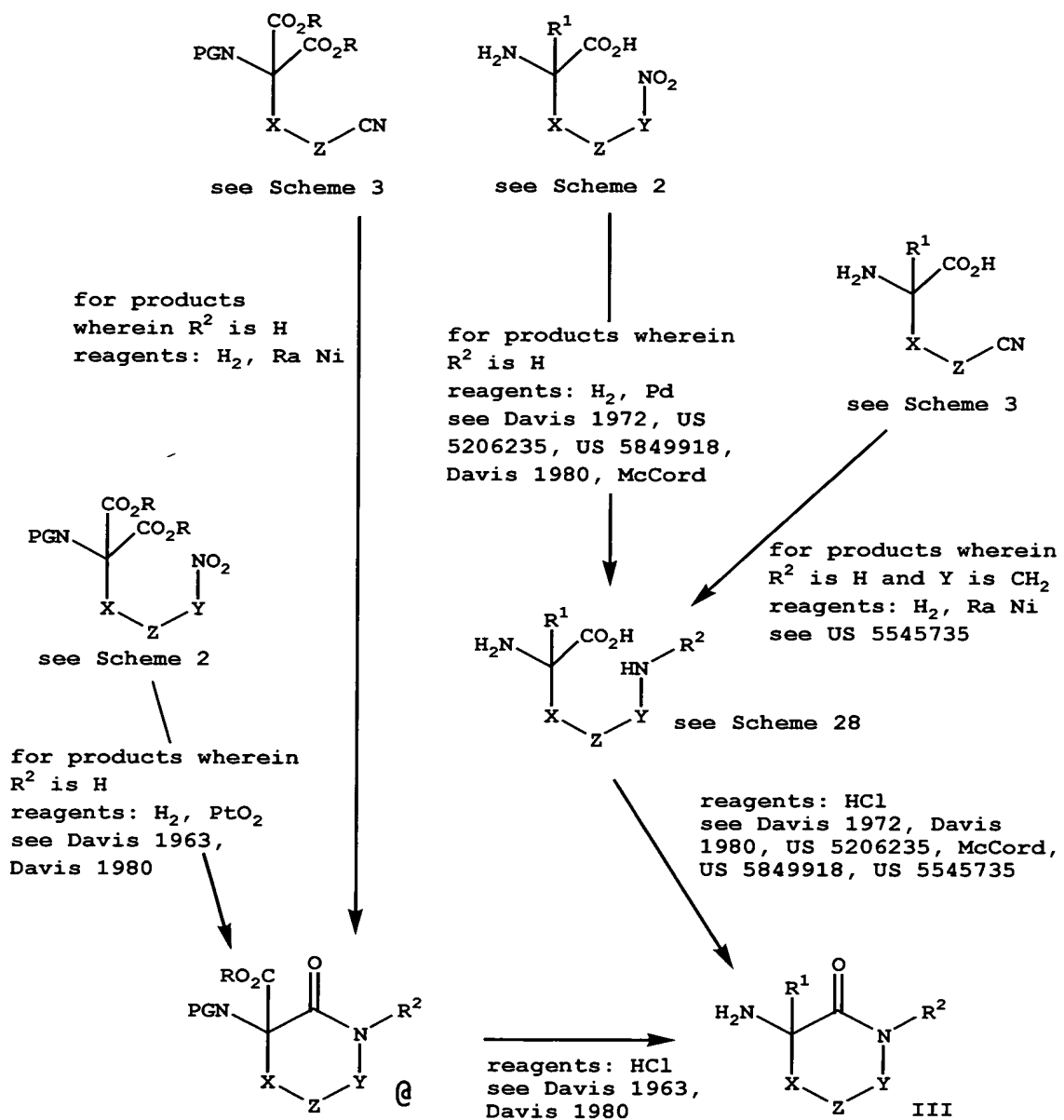
SCHEME 2

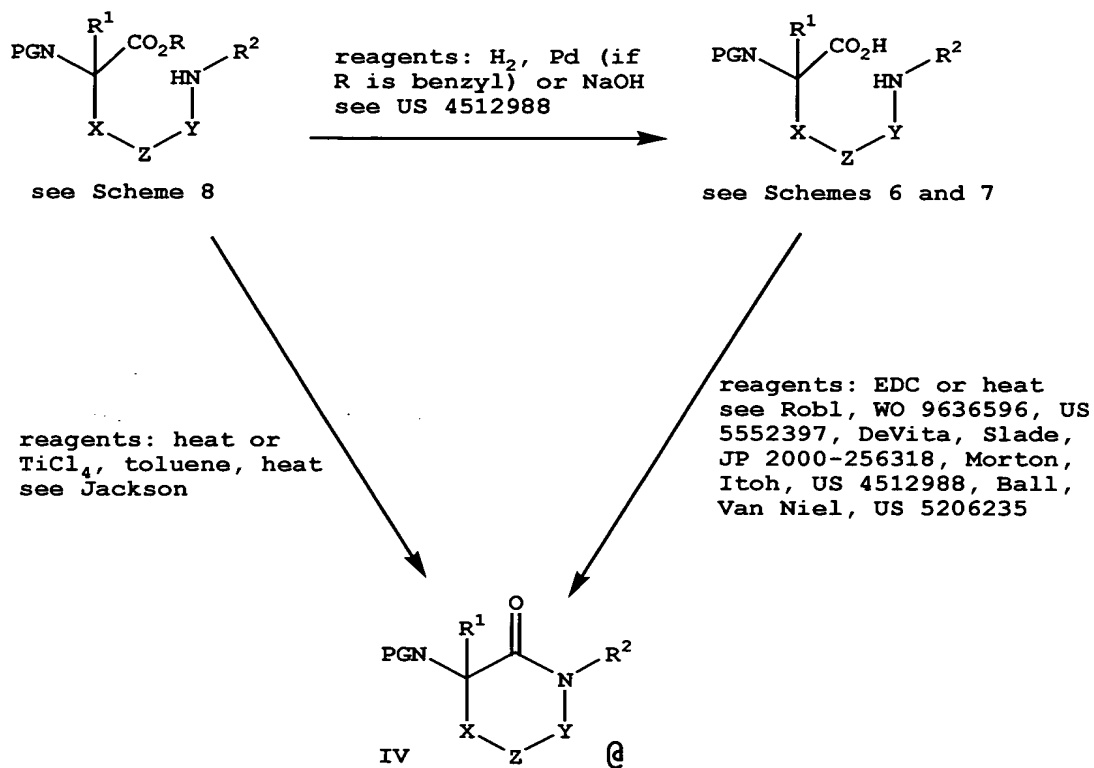


SCHEME 3

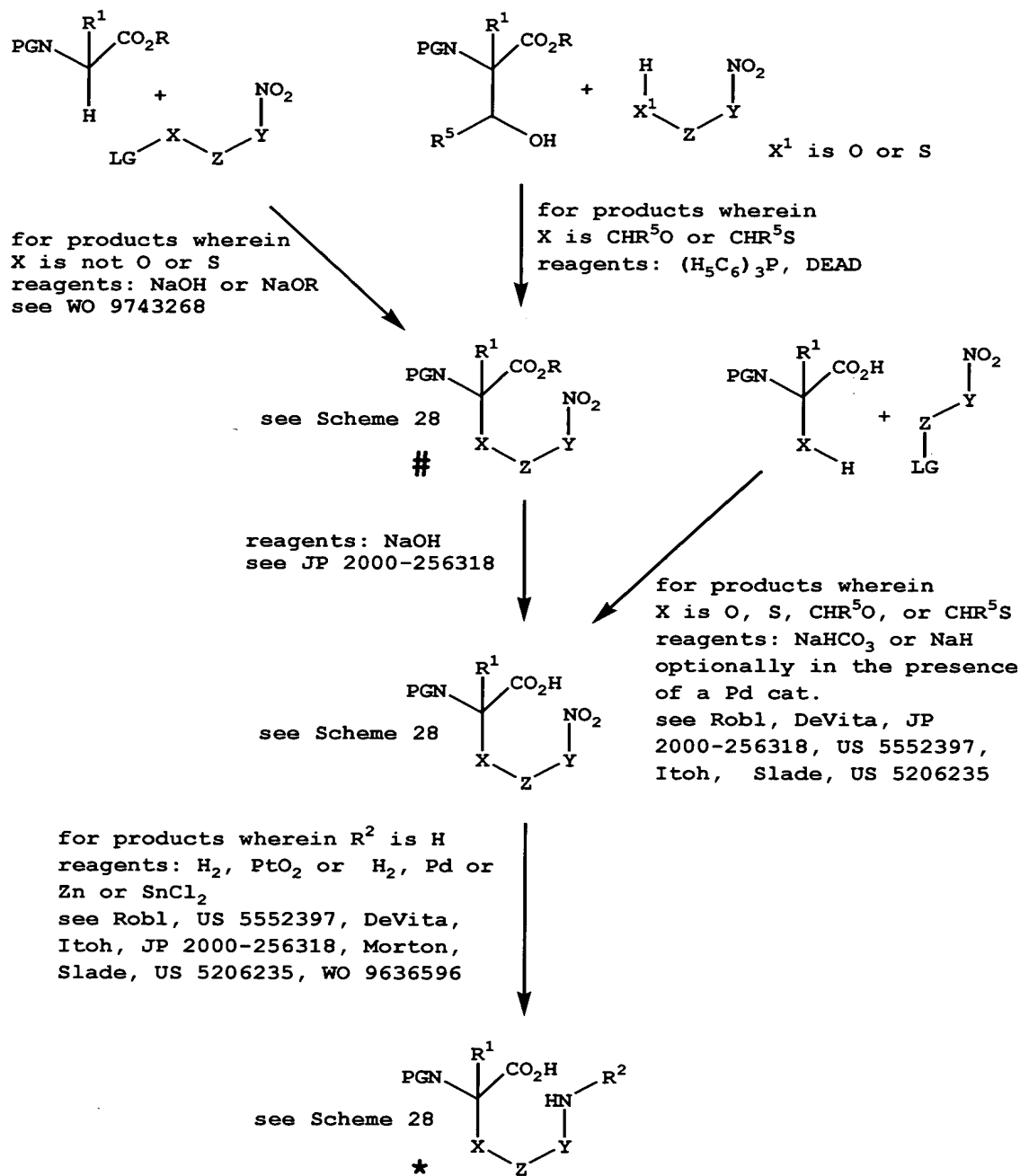


SCHEME 4

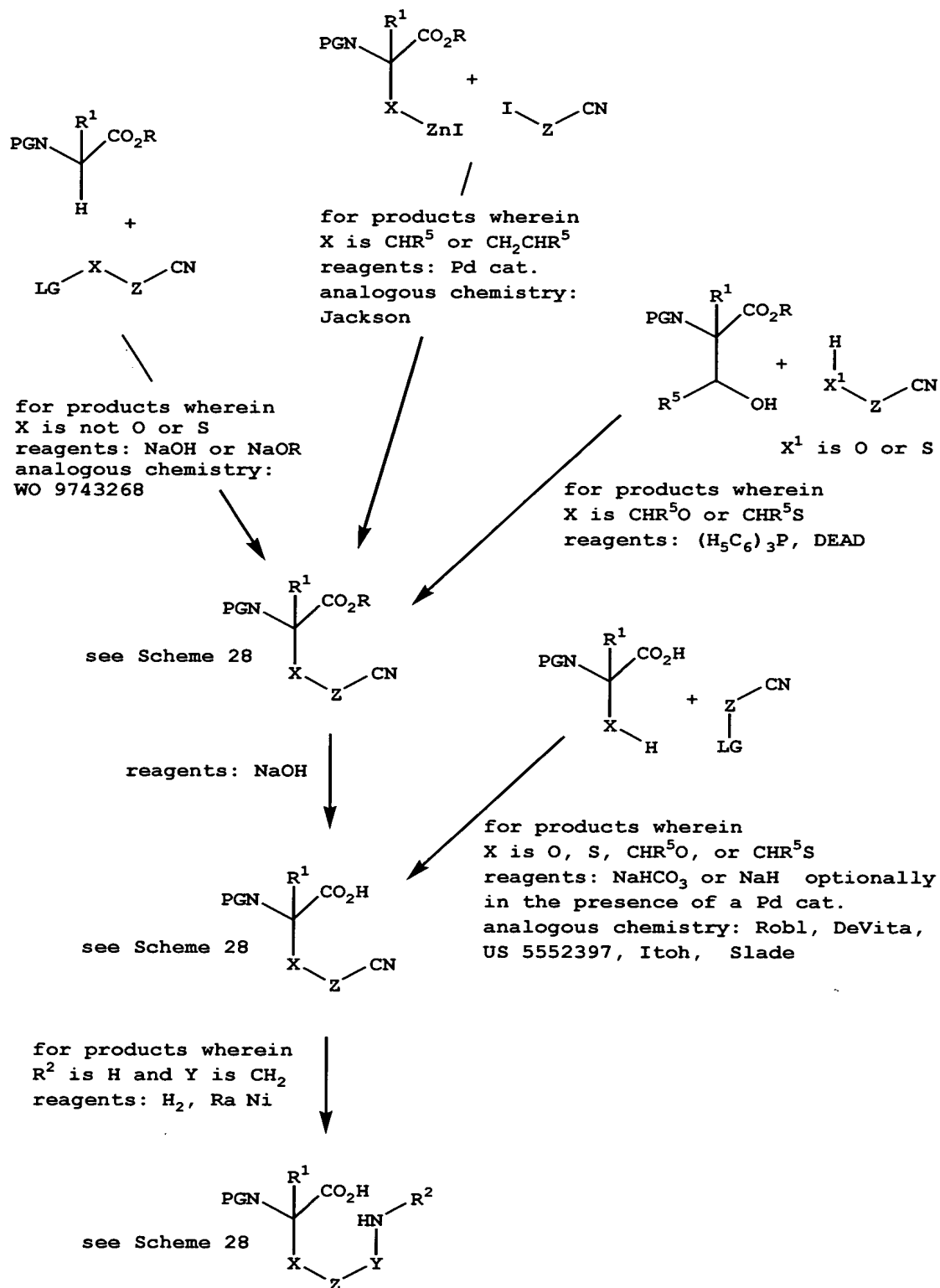


SCHEME 5

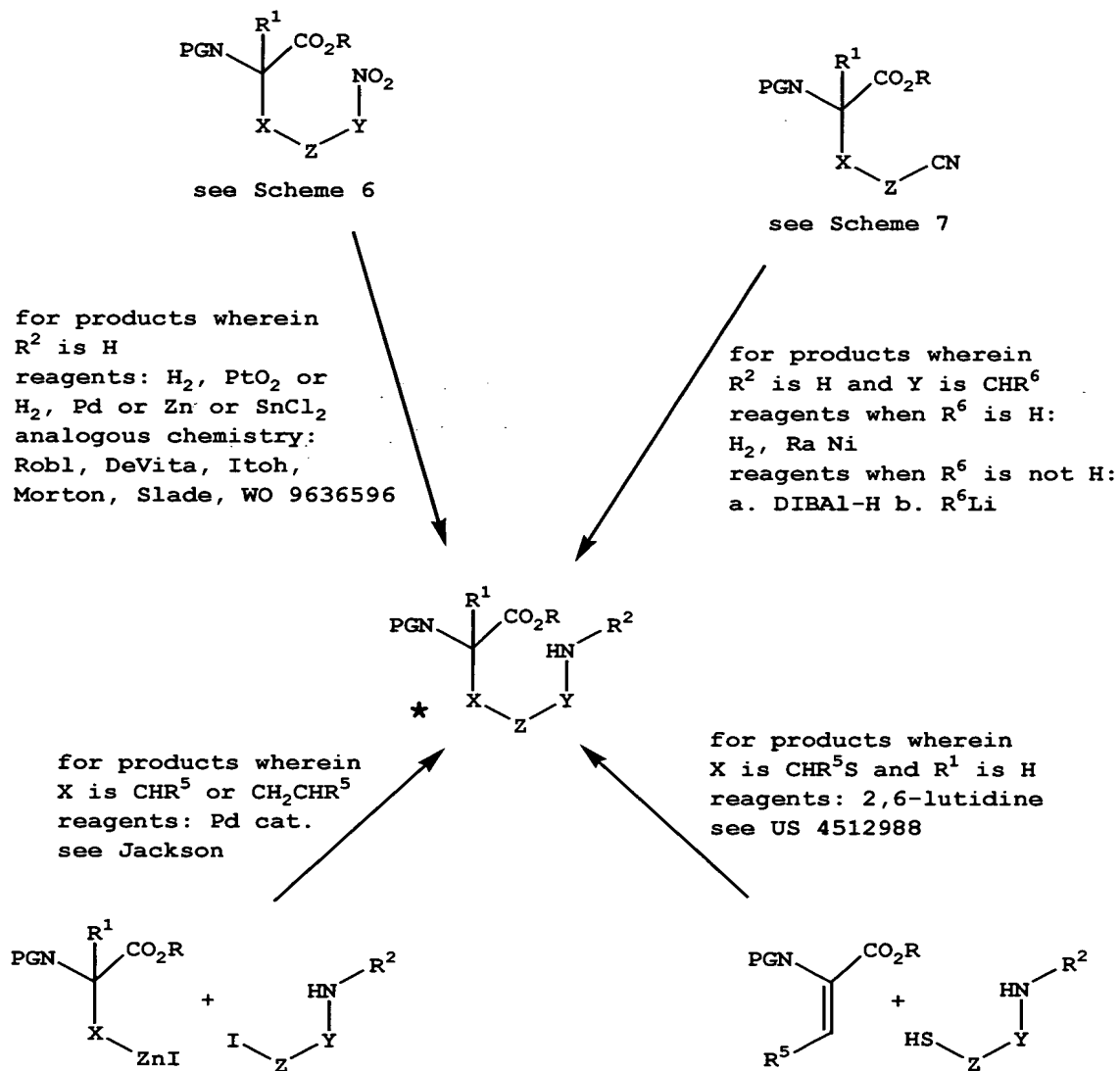
SCHEME 6



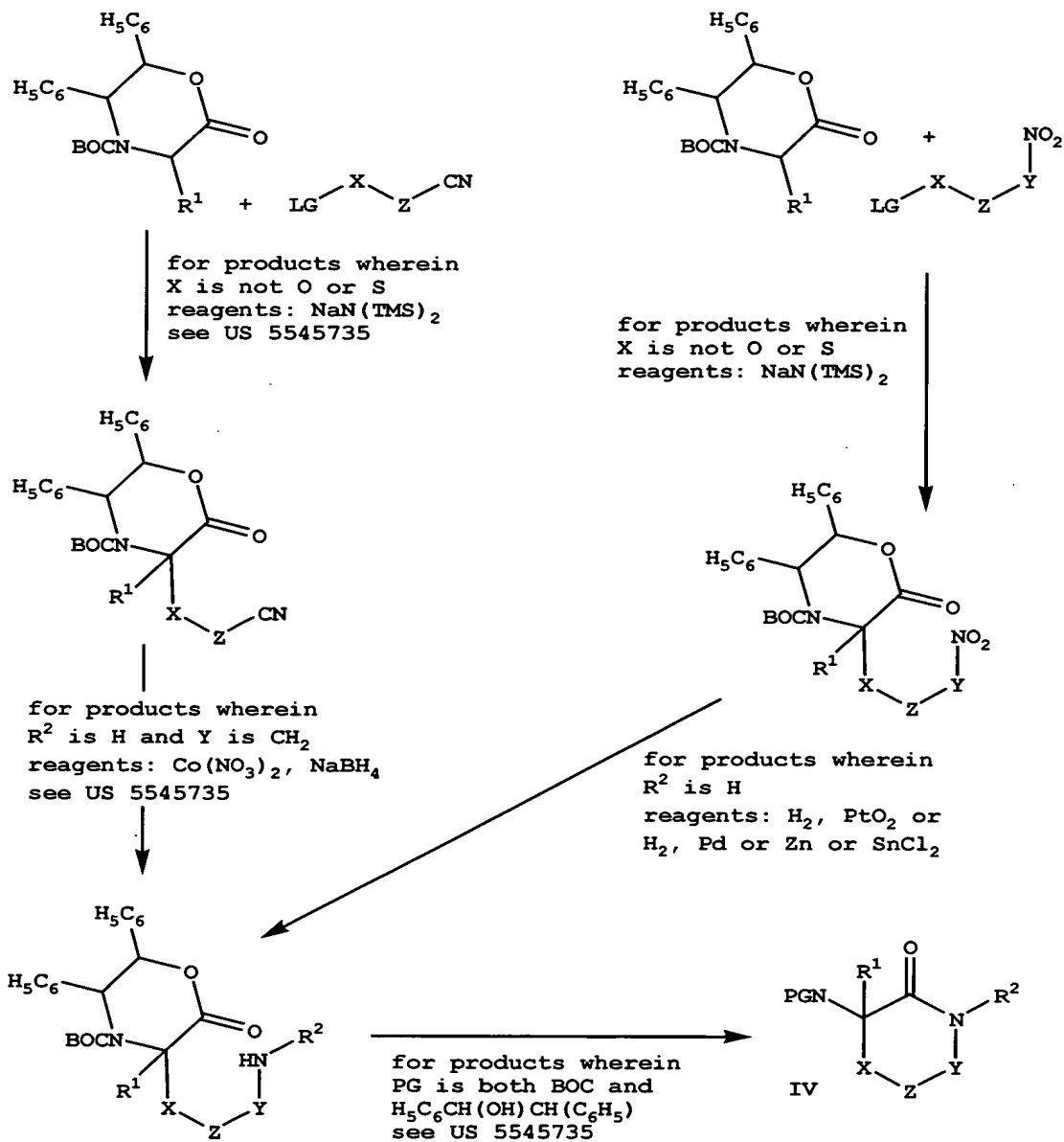
SCHEME 7



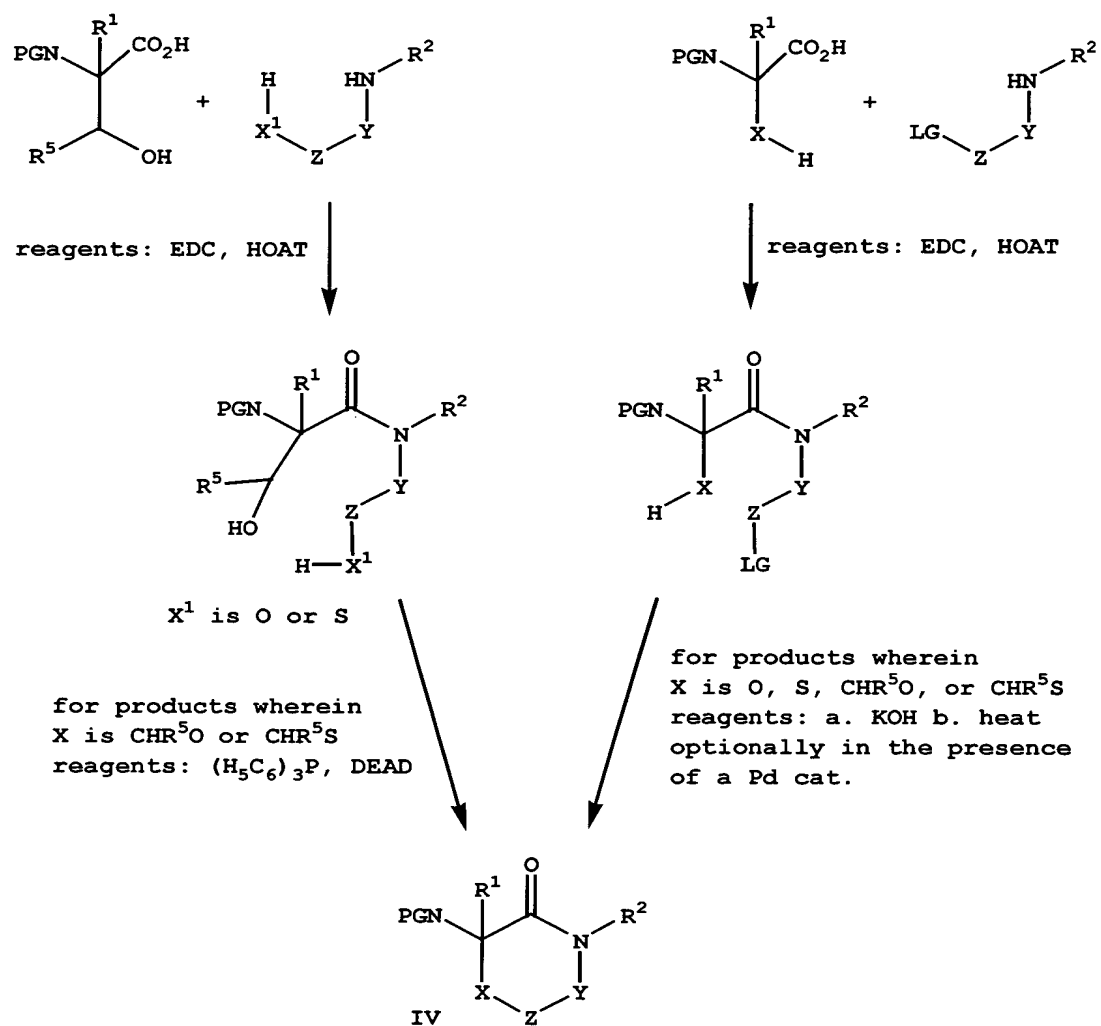
SCHEME 8



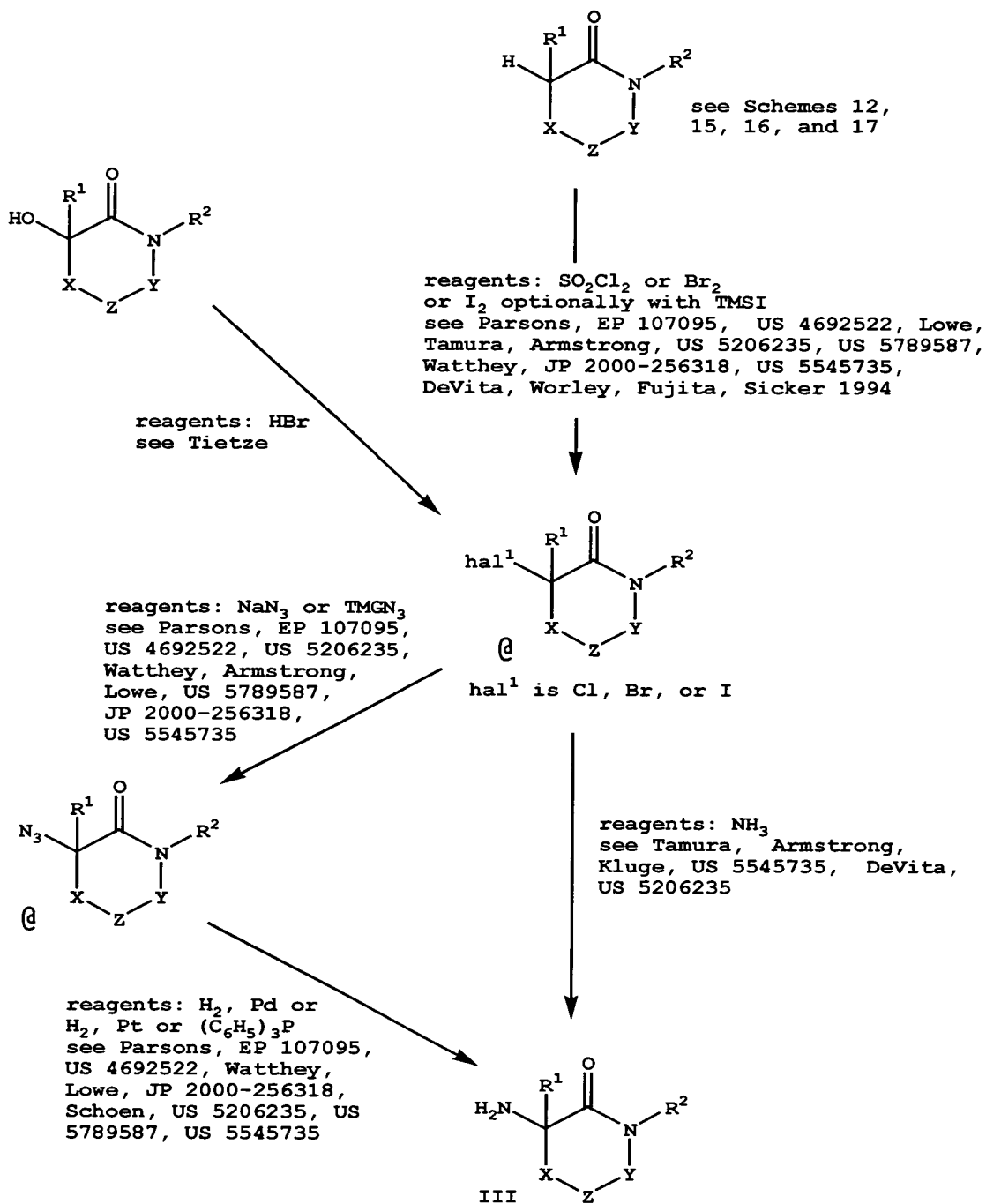
SCHEME 9



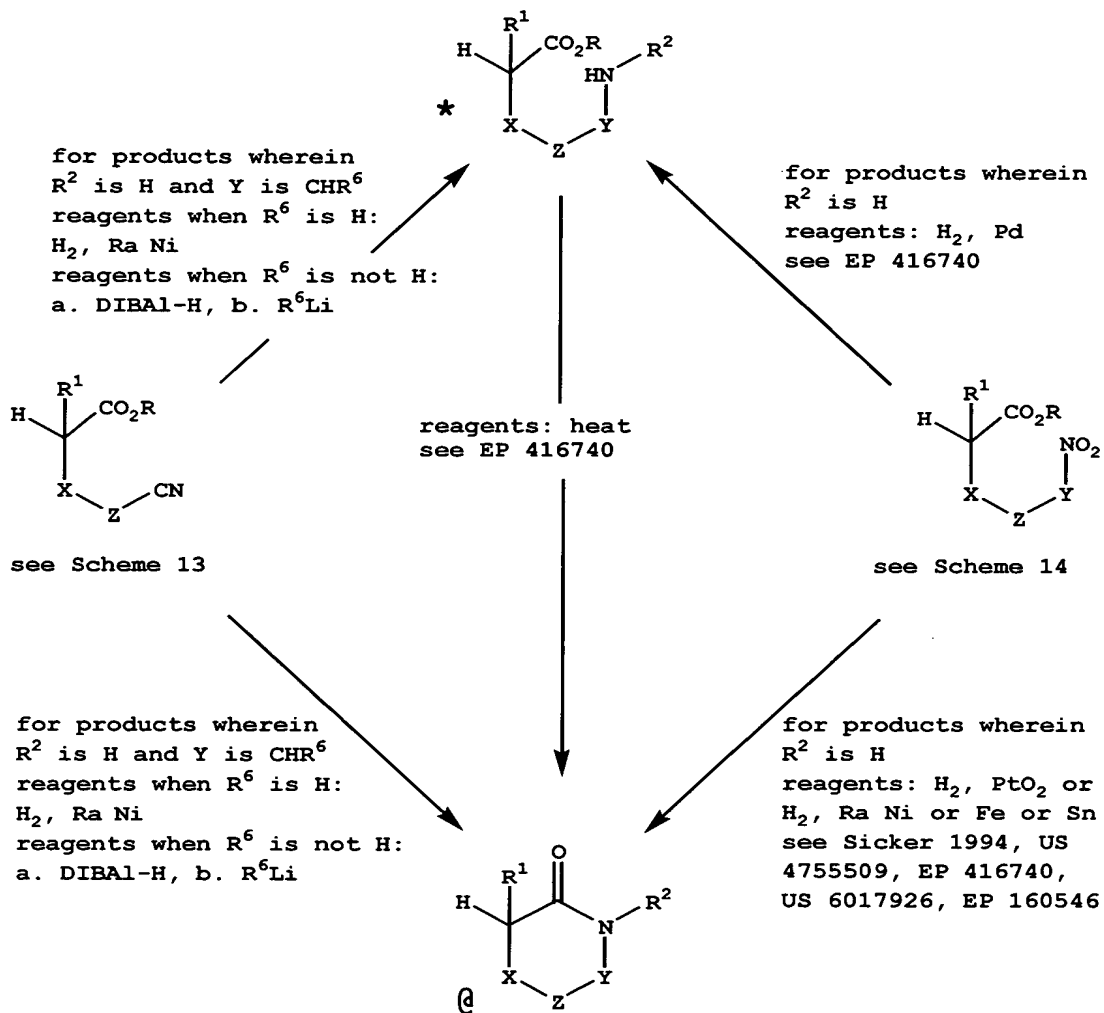
SCHEME 10

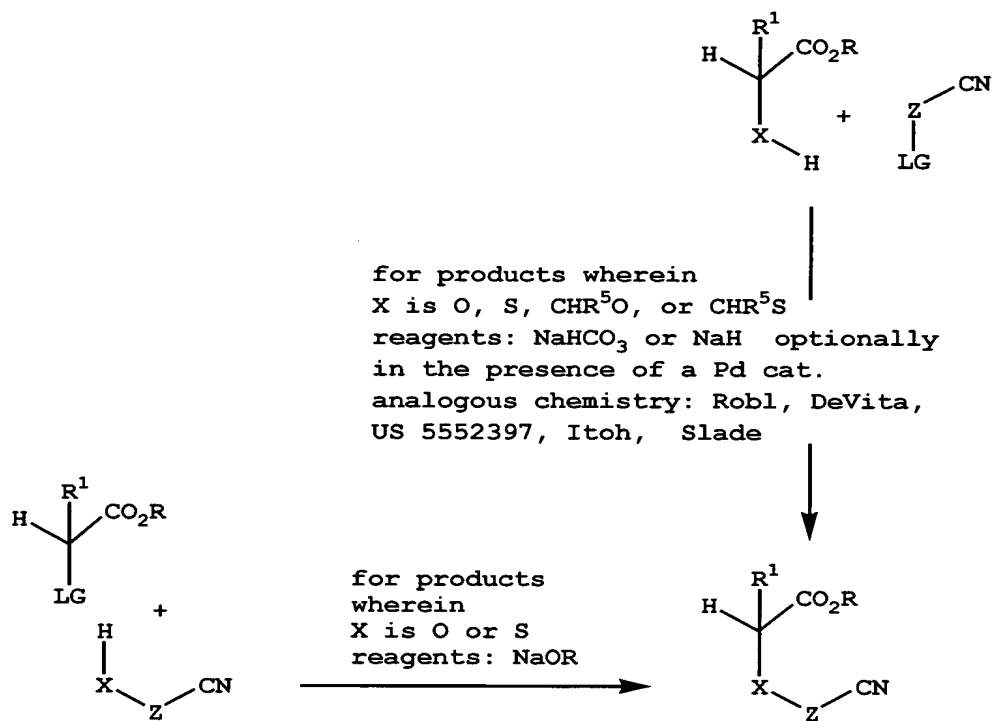


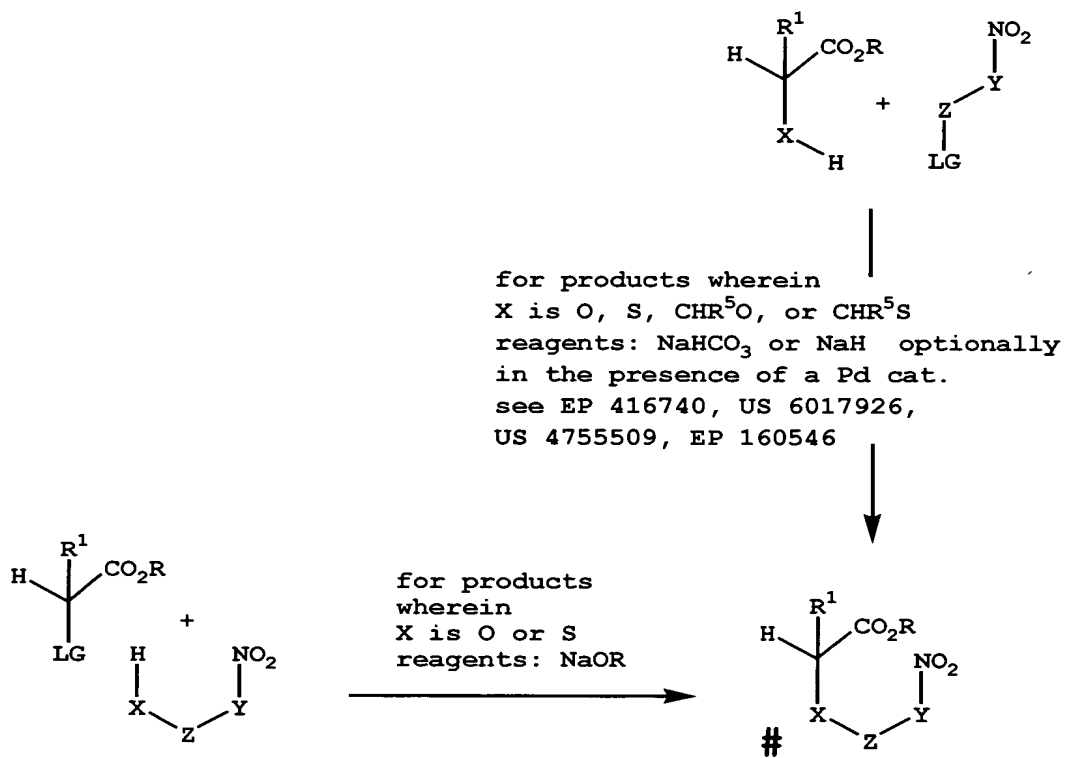
SCHEME 11



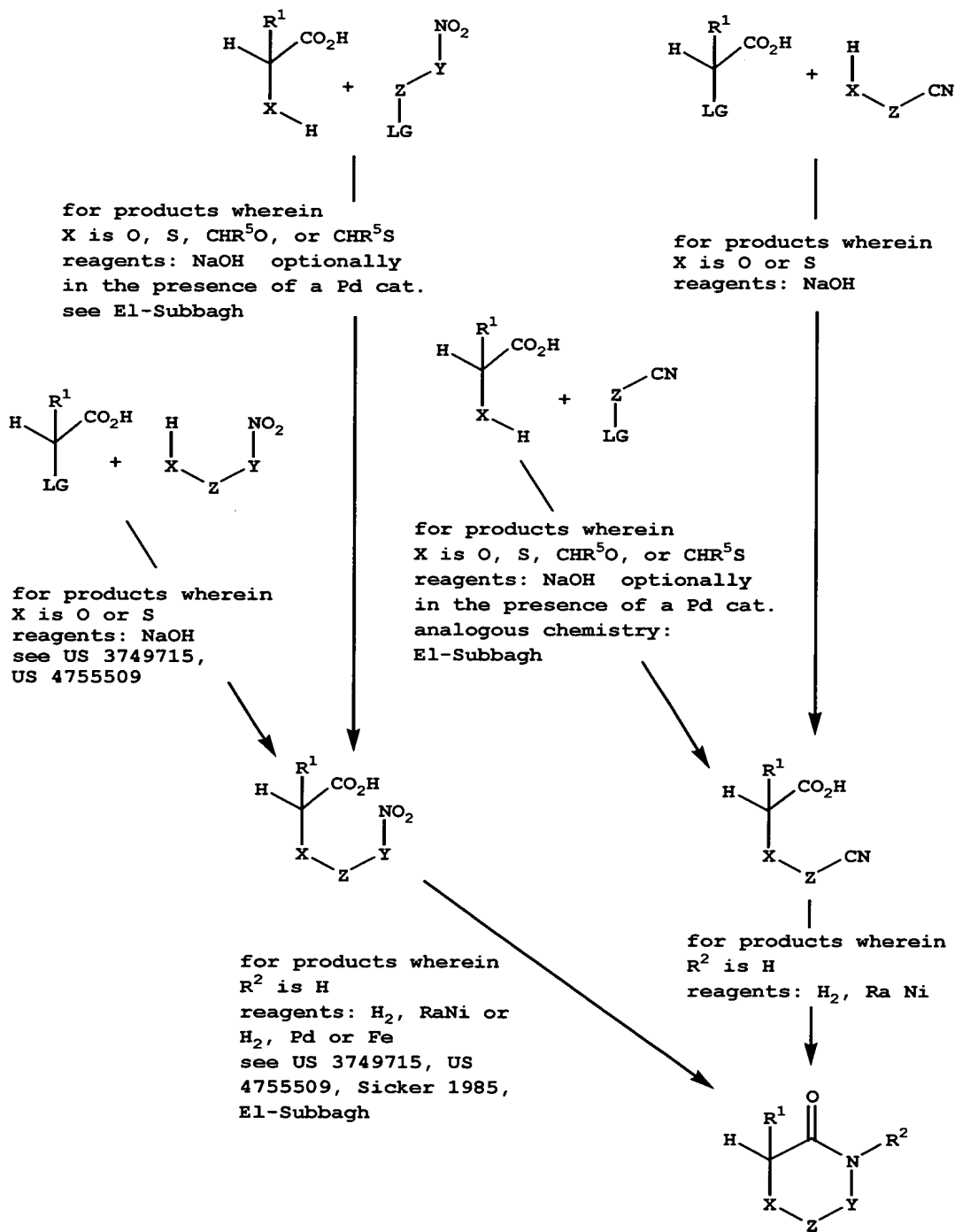
SCHEME 12



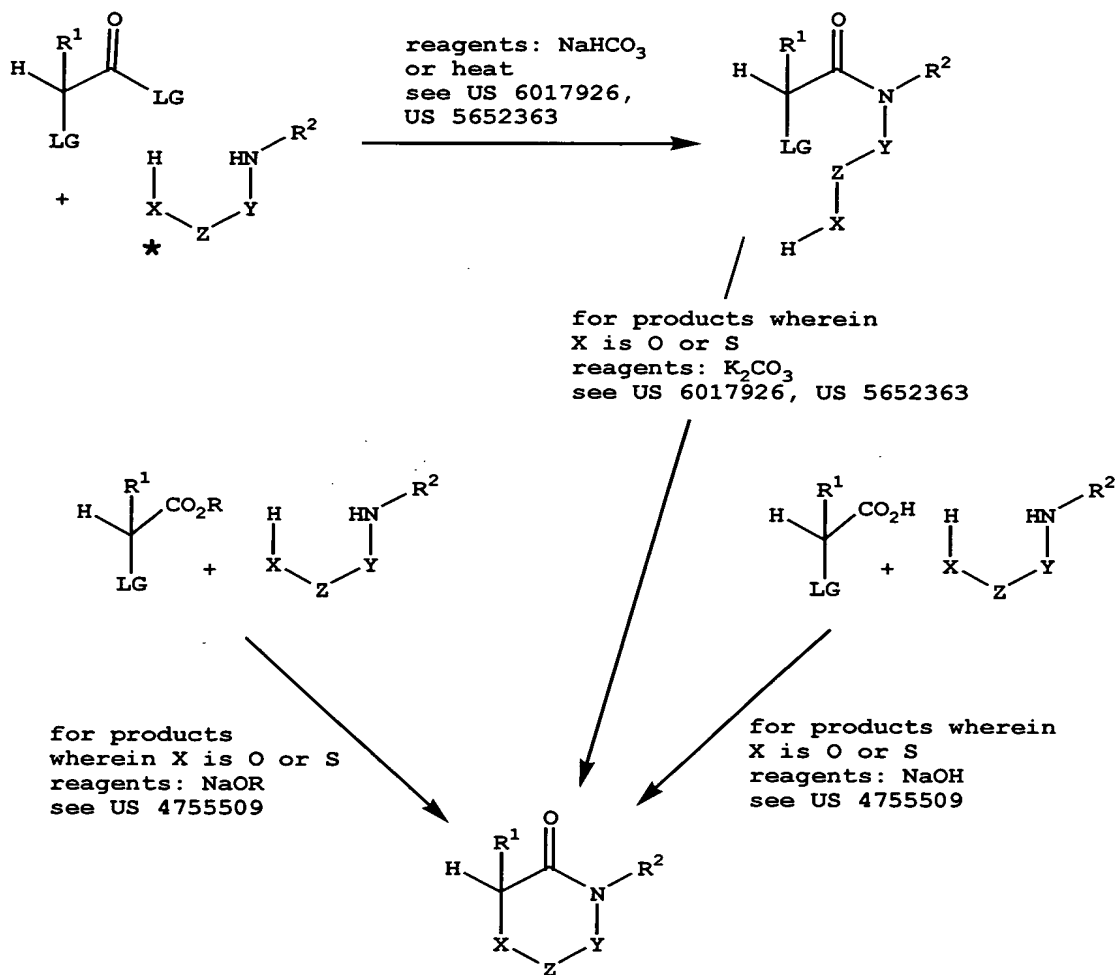
SCHEME 13

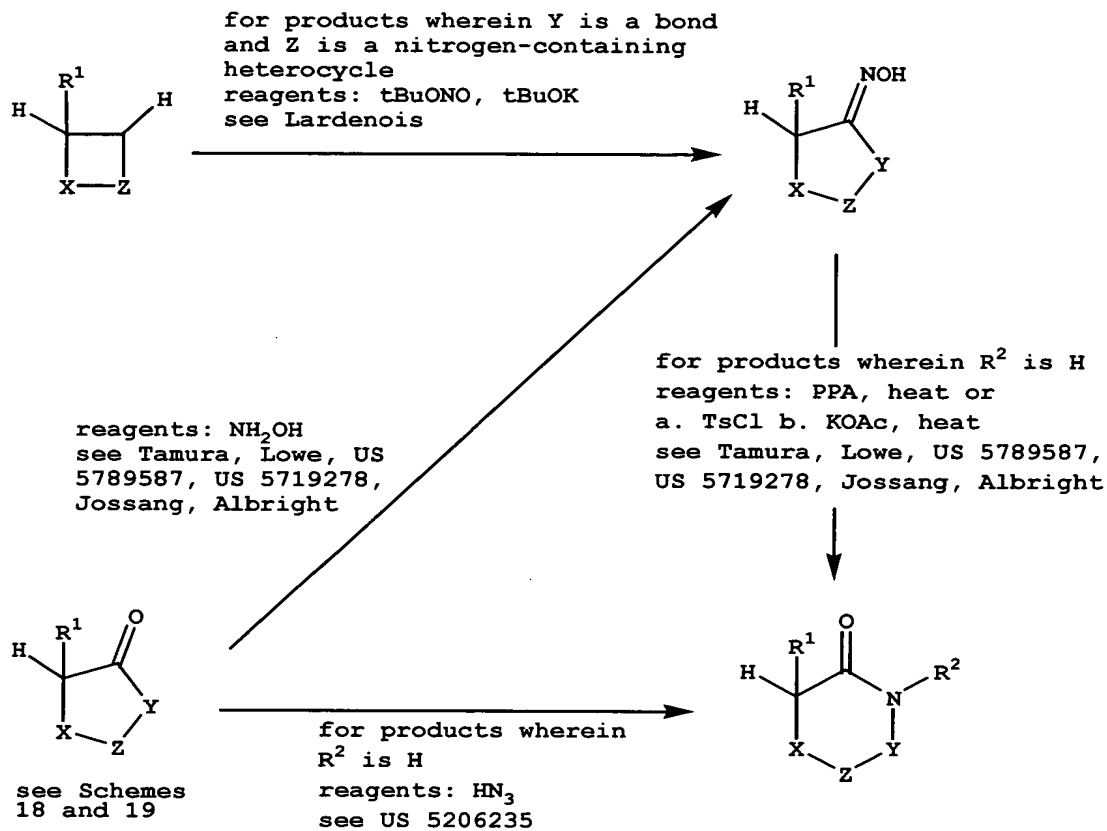
SCHEME 14

SCHEME 15

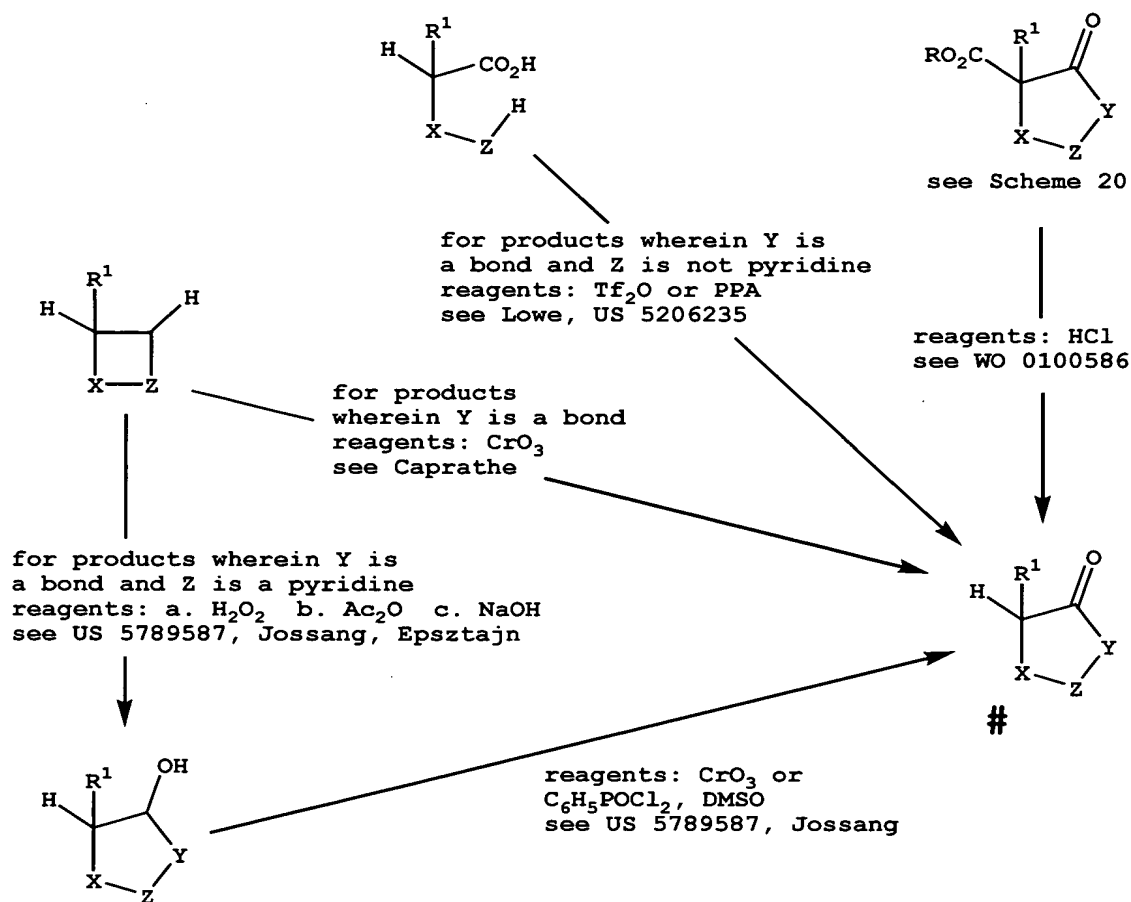


SCHEME 16

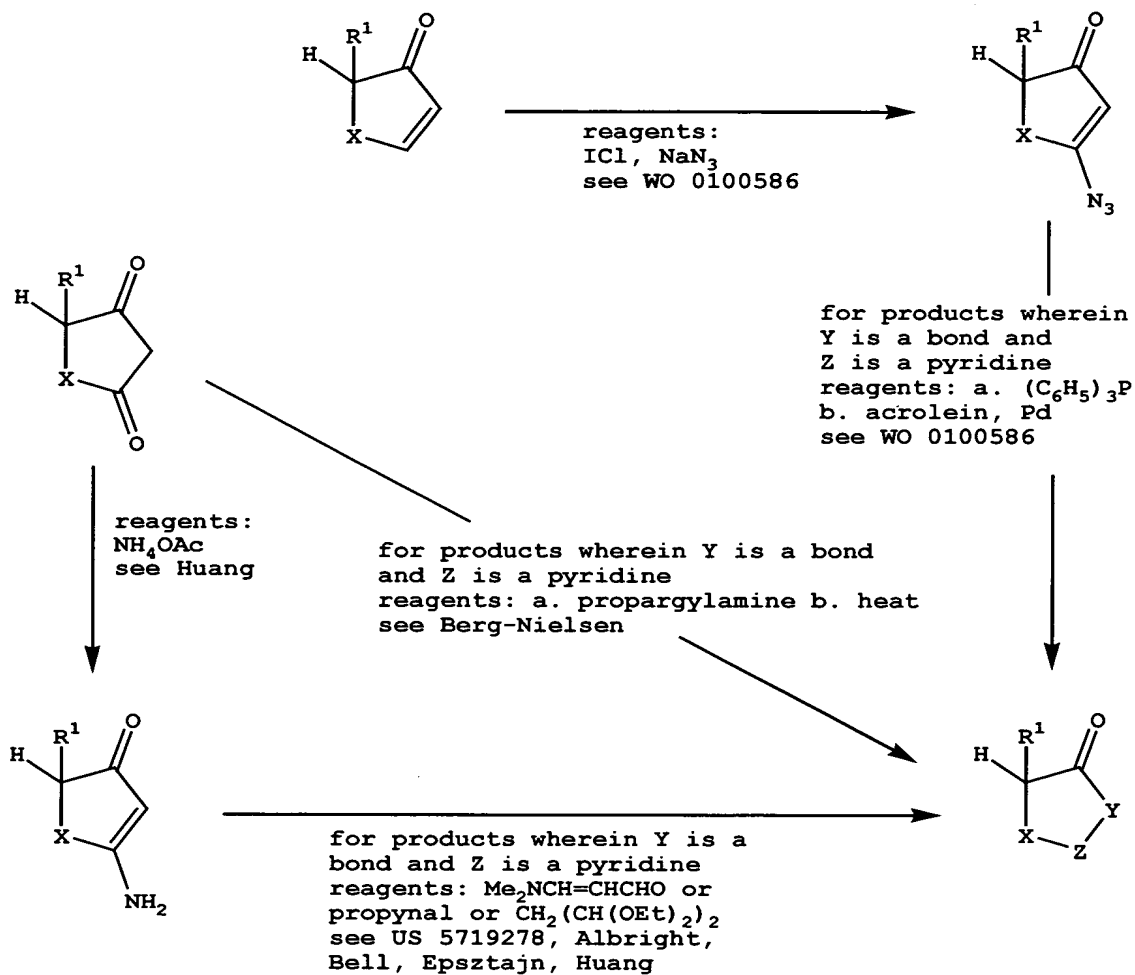


SCHEME 17

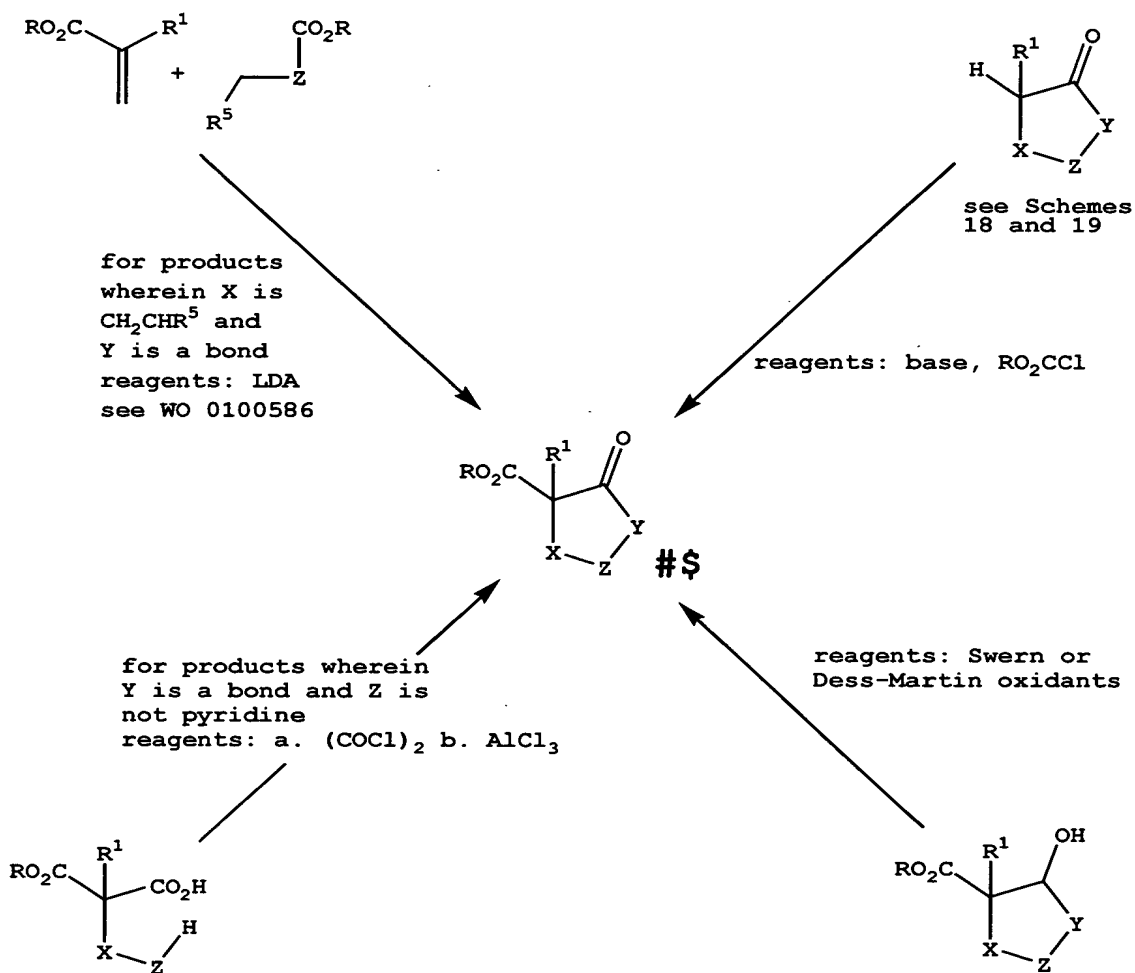
SCHEME 18

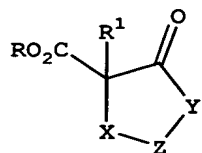


SCHEME 19



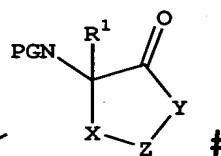
SCHEME 20



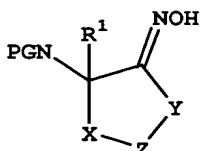
SCHEME 21

see Scheme 20

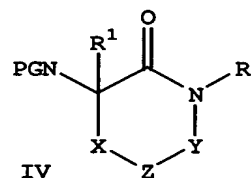
for products wherein
PG is RO₂C
reagents: (Curtius degradation)
a. NaOH b. SOCl₂
c. NaN₃ d. ROH, heat

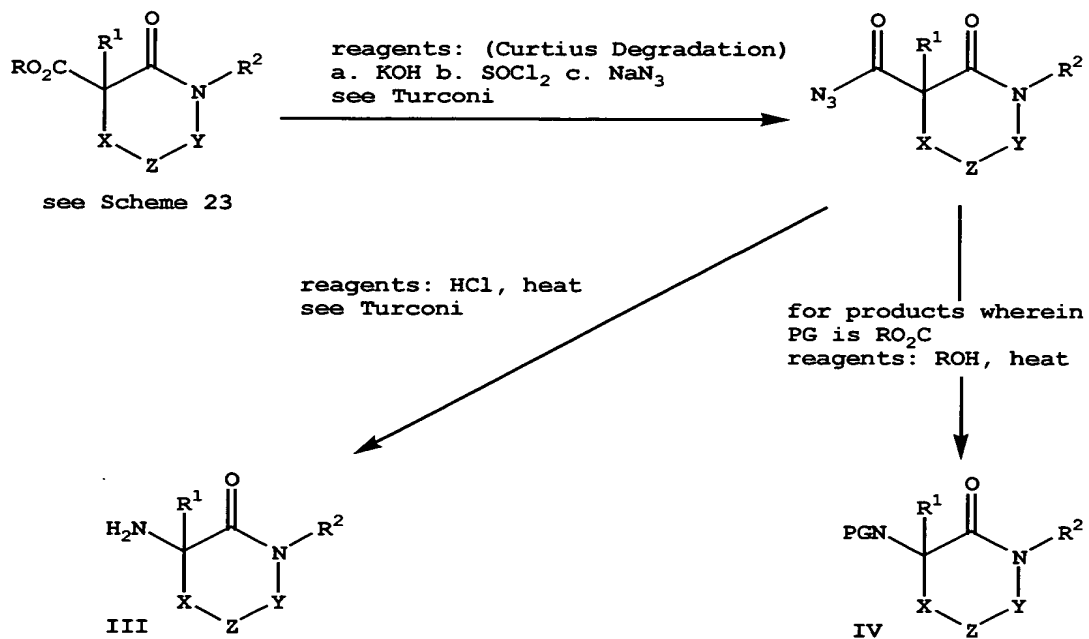


reagents: NH₂OH
analogous chemistry:
Tamura, Lowe,
Jossang, Albright

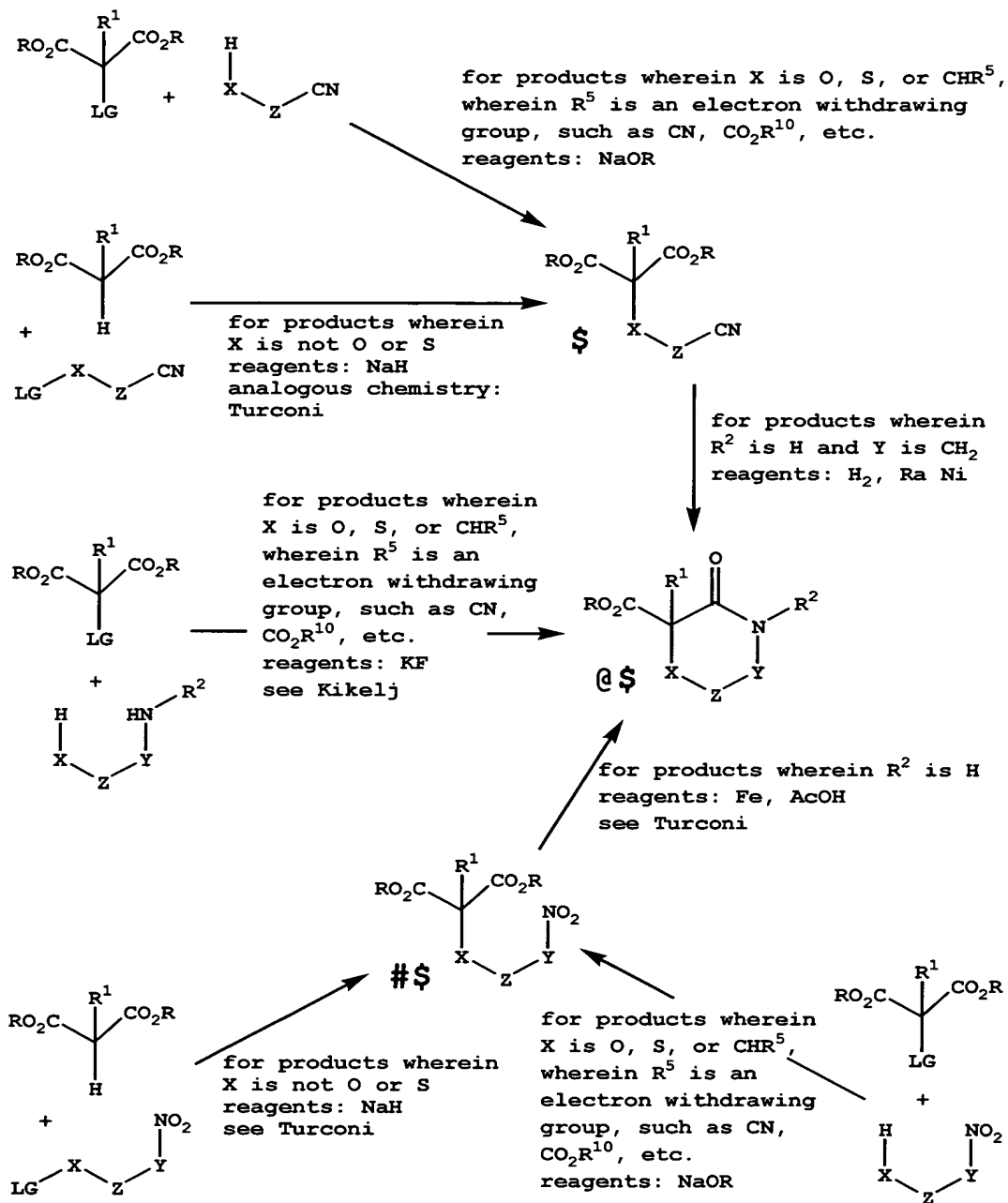


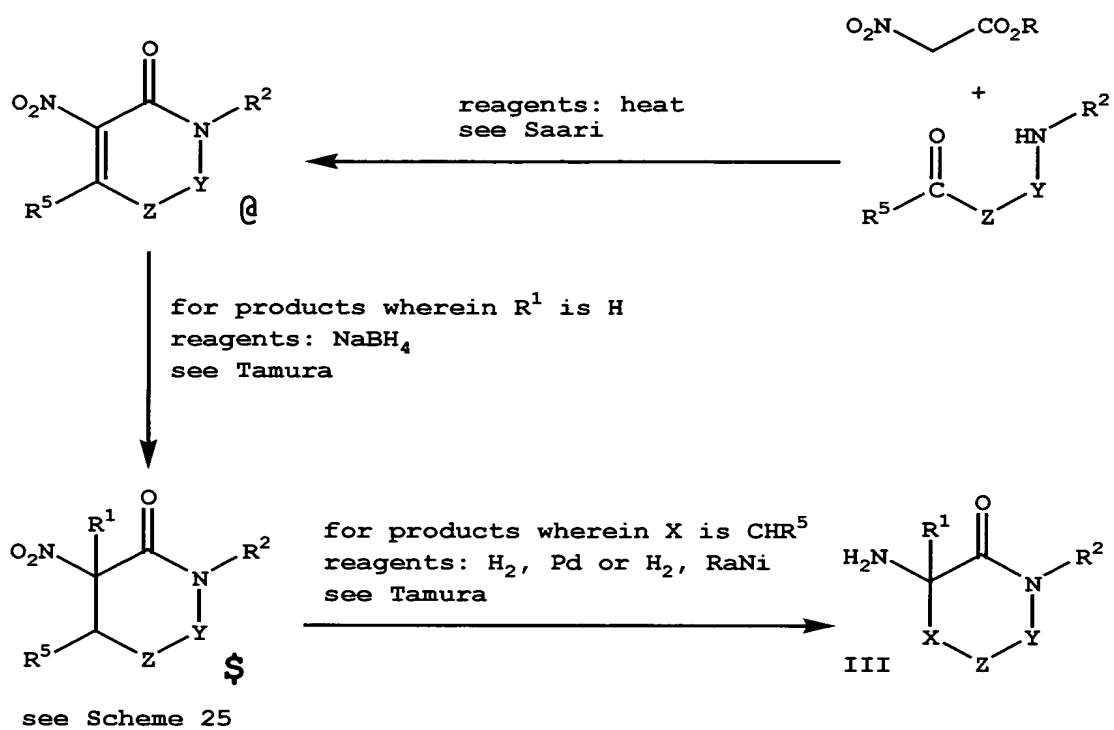
for products wherein R² is H
reagents: PPA, heat or
a. TsCl b. KOAc, heat
analogous chemistry:
Tamura, Lowe, Jossang, Albright

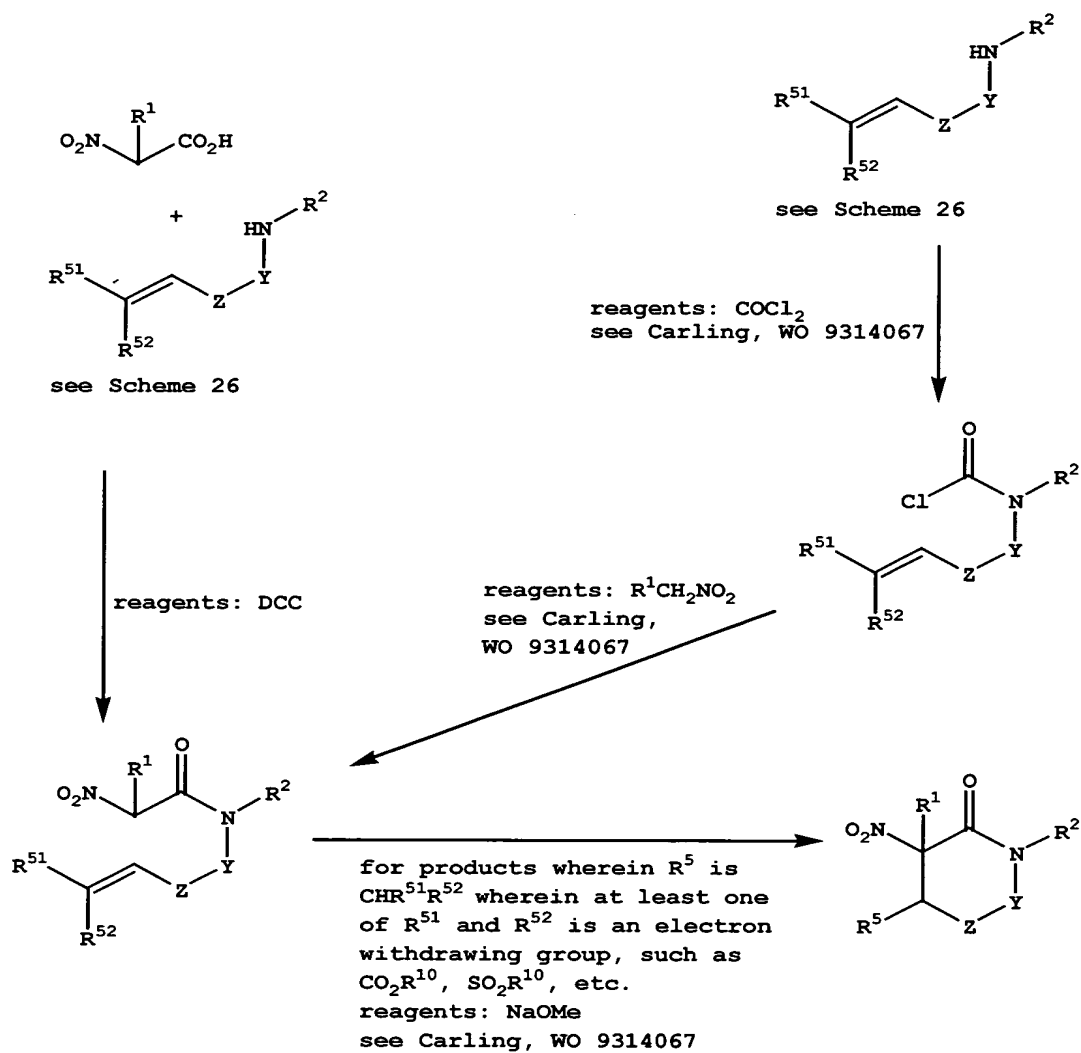


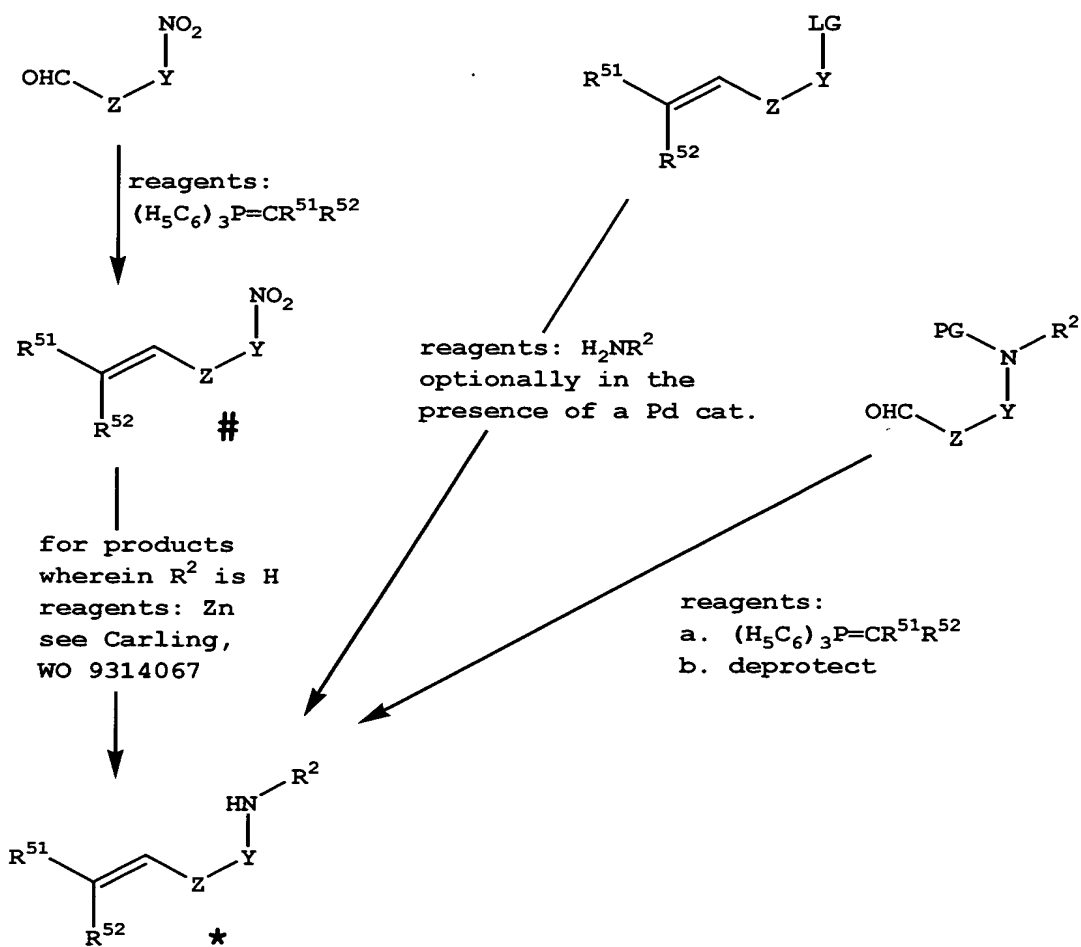
SCHEME 22

SCHEME 23

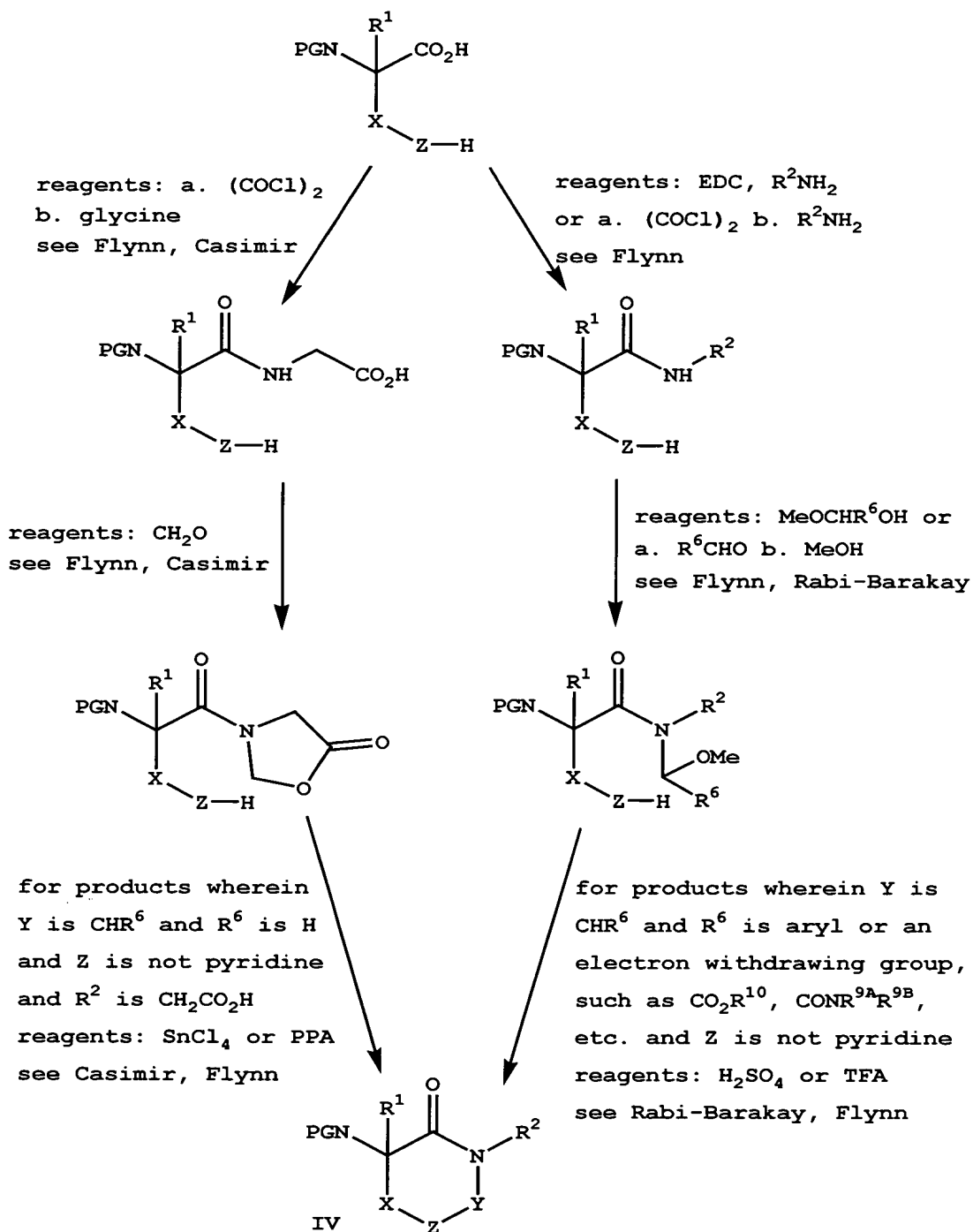


SCHEME 24

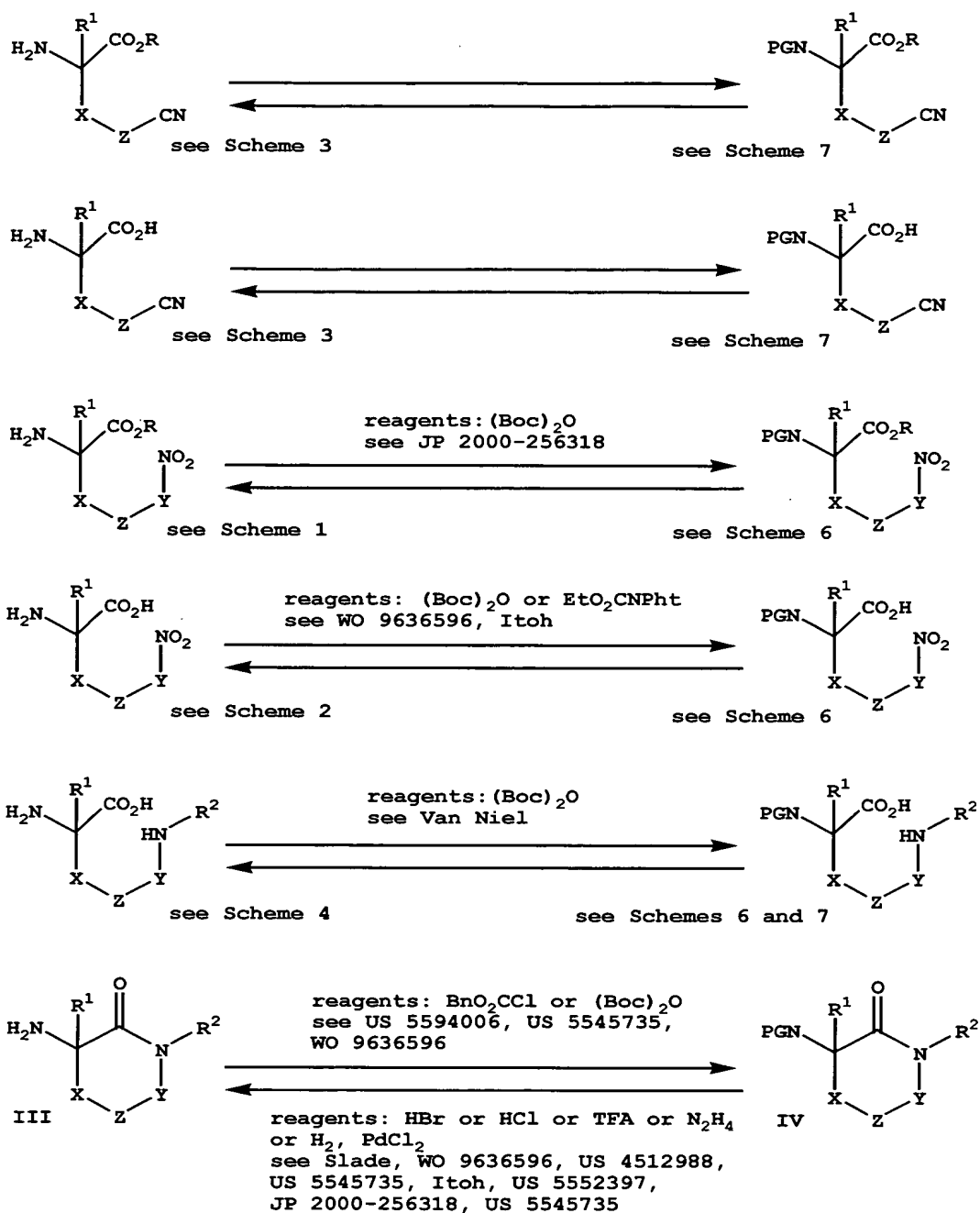
SCHEME 25

SCHEME 26

SCHEME 27



SCHEME 28



In the synthetic schemes above the reagent lists are abbreviated. References cited provide full details and in some cases alternative reagents. It is understood
5 that the reagents shown in the synthetic schemes are example reagents, not meant to be limiting. Those skilled in the art will recognize that there are many acids (hydrochloric acid, polyphosphoric acid, etc.), many bases (sodium hydride, potassium methoxide, etc.),
10 many oxidants (hydrogen peroxide, 3-chloroperoxybenzoic acid, etc.), many hydrogenation catalysts (palladium, platinum oxide, Raney[®] Nickel, etc.), and so on that may be employed to synthesize the compounds of the invention. In some cases alternative reagents known to those skilled
15 in the art will be superior to those listed in the synthetic schemes. Alternative reagents may be found in Reagents For Organic Synthesis (Fieser and Fieser, John Wiley & Sons) and Compendium of Organic Synthetic Methods (John Wiley & Sons).

20 In the synthetic schemes LG represents a leaving group, for example fluoride, bromide, methanesulfonate or trifluoromethanesulfonate. The group R as utilized in the above schemes, (lacking a superscripted numeral) represents an alkyl or benzyl group.

25 In the synthetic schemes the possibility that certain compounds may be transformed from one variant of the structure to another variant of the same structure is denoted by the appearance of one or more of the following symbols next to the structure: \$, *, @, #.

30 These symbols appear only at the first instance of the intermediate structure to which they pertain. The meaning of these symbols is as follows:

Intermediates denoted \$ in which R¹ is an unsubstituted or substituted alkyl or alkenyl group may
35 be prepared from the corresponding intermediates denoted \$ in which R¹ is hydrogen by treatment with a base such

as sodium hydride and the appropriate unsubstituted or substituted alkylating or alkenylating agent.

Intermediates denoted * in which R^2 is $R^{21}R^{22}CH$ (R^{21} and R^{22} are independently defined in the same manner as R^2) may be prepared from the corresponding intermediates denoted * in which R^2 is hydrogen by reductive amination with a ketone or aldehyde $R^{21}R^{22}CO$ and a reducing agent, such as sodium cyanoborohydride in the presence of an acid, such as acetic acid.

Intermediates denoted * in which R^2 is aryl may be prepared from the corresponding intermediates denoted * in which R^2 is hydrogen by palladium catalyzed coupling with an aryl halide, as described in Hamann, et al., J. Am. Chem. Soc. 1998, 120, 7369-7370 and references contained therein, and in recent papers authored by John F. Hartwig.

Compounds of formula Ib and intermediates denoted @ in which R^2 is an unsubstituted or substituted alkyl or alkenyl group may be prepared from the corresponding compounds of formula Ib and intermediates denoted @, respectively, in which R^2 is hydrogen by treatment with a base, such as sodium hydride and the appropriate unsubstituted or substituted alkylating or alkenylating agent.

Intermediates denoted # in which Y is CH_2R^6 and R^6 is an unsubstituted or substituted alkyl or alkenyl group may be prepared from the corresponding intermediates denoted # in which Y is CH_2 by treatment with a base such as sodium hydride and the appropriate unsubstituted or substituted alkylating or alkenylating agent.

In several synthetic schemes alpha amino acids or protected alpha amino acids are shown as intermediates or serve as starting materials. Many methods for the preparation of alpha amino acids and protected alpha amino acids are described in, or referenced in: Jackson, et al., J. Org. Chem. 1998, 63, 7875-7884; Ferraris, et

al., J. Am. Chem. Soc. 2002, 124, 67-77; Fu, et al., J. Org. Chem. 2001, 66, 7118-7124.

Schemes 1-4 outline the preparation of amines III with late formation of the lactam amide bond. Schemes 5-9 outline the preparation of protected amines IV with late formation of the lactam amide bond. Scheme 10 outlines the preparation of protected amines IV with late formation of the X-Z bond. Schemes 11-20 outline the preparation of amines III with late introduction of the amino group via halogenation of the desamino intermediate. Scheme 21 outlines the preparation of protected amines IV with late expansion of a cyclic ketone to the lactam ring. Schemes 22-23 outline the preparation of amines III and protected amines IV with late Curtius degradation to install the amino group. Schemes 24-26 outline the preparation of protected amines IV with late formation of the X-C α bond. Scheme 27 outlines the preparation of protected amines IV with late formation of the Y-Z bond. Scheme 28 identifies a set of amine and amine-protected intermediates that may be particularly usefully interconverted using standard amine protecting group chemistry as described in Protective Groups in Organic Synthesis.

Compounds of formula Ib and protected amines IV wherein R⁷ or R⁸ is other than hydrogen, halo, trifluoromethyl, or hydroxy, may be prepared from compounds of formula Ib and protected amines IV wherein R⁷ or R⁸, respectively, is halo or hydroxy, using various palladium catalyzed coupling procedures as described in Aranyos, et al., J. Am. Chem. Soc. 1999, 121, 4369-4378 and Hamann, et al., J. Am. Chem. Soc. 1998, 120, 7369-7370 and references contained therein, and in recent papers authored by Gregory C. Fu, Stephen L. Buchwald, or John F. Hartwig. These procedures are directly applicable when R⁷ or R⁸ is halo. When R⁷ or R⁸ is hydroxy, prior activation by conversion of the hydroxyl group to a

trifluoromethylsulfonyloxy group, as described in the
aforementioned references, is required.

Compounds of formula Ib and protected amines IV in
which R⁷ or R⁸ is substituted or unsubstituted alkoxy or
5 aryloxy may be prepared by elaboration of the analogous
compounds of formula Ib and protected amines IV wherein
R⁷ or R⁸, respectively, is hydroxy. For instance, a
compound where R⁷ or R⁸ is carbomethoxymethoxy may
prepared from the compound in which R⁷ or R⁸ is hydroxy by
10 alkylation with methyl bromoacetate. A compound where R⁷
or R⁸ is carboxymethoxy may be prepared by hydrolysis of
the compound where R⁷ or R⁸ is carbomethoxymethoxy or
carbo-t-butyloxymethoxy. A compound where R⁷ or R⁸ is 2-
hydroxyethoxy may be prepared by reduction of the
15 compound where R⁷ or R⁸ is carbomethoxymethoxy or
carboxymethoxy. A compound where R⁷ or R⁸ is 2,3-
dihydroxypropyloxy may be prepared from the compound
where R⁷ or R⁸ is hydroxy by alkylation with glycidyl 3-
nitrobenzenesulfonate, followed by epoxide hydrolysis. A
20 compound where R⁷ or R⁸ is aryloxy may be prepared from
the compound in which R⁷ or R⁸ is hydroxy and an aryl
halide by various palladium catalyzed coupling procedures
as described in Aranyos, et al., J. Am. Chem. Soc. 1999,
121, 4369-4378 and references contained therein, and in
25 recent papers authored by Stephen L. Buchwald.

Compounds of formula Ib and protected amines IV in
which Z is a pyridine N-oxide may be prepared from the
corresponding compounds of formula Ib and protected
amines IV in which Z is a pyridine by oxidation with an
30 oxidizing agent, for example 3-chloroperoxybenzoic acid,
in a solvent such as dichloromethane.

Compounds of formula Ib and protected amines IV in
which X is SO₂ or CHR⁵SO₂ may be prepared from the
corresponding compounds of formula Ib and protected
amines IV in which X is S or CHR⁵S, respectively, by
35 oxidation with an oxidizing agent, for example m-
chlorobenzoic acid, in a solvent such as dichloromethane.

In general, the interchange of functional groups within R^1 , R^2 , R^5 , R^6 , R^7 and R^8 , including the formation of various hydrogen bonding groups, may be accomplished according to the methods and procedures described in

5 Compendium of Organic Synthetic Methods (John Wiley & Sons) and Comprehensive Organic Transformations - A Guide To Functional Group Preparations (R. C. Larock, VCH Publishers, 1989). It is understood that during the course of manipulating any functional group within R^1 , R^2 ,

10 R^5 , R^6 , R^7 and R^8 , standard protecting groups, as described in Protective Groups in Organic Synthesis, may be employed to avoid undesired reaction of any other functional group, or of the lactam at its carbonyl or nitrogen, particularly when R^2 is hydrogen, or of the

15 indole ring or other bicyclic heterocycle W, particularly at its nitrogen, or of the amide linking the lactam containing ring to W. Standard protecting groups may be used for this purpose at any stage of the synthesis, for example in manipulating a functional group to convert one

20 compound of formula Ib to another compound of formula Ib, or in manipulating a functional group to convert one protected amine IV to another amine IV, or to avoid undesired reaction during the coupling of carboxylic acid II and amine III, or during the sequence of steps leading

25 to the formation of either carboxylic acid II or protected amine IV.

The references provided within the synthetic schemes herein are not intended to constrain the applicability of the reaction steps, but rather to exemplify the reaction

30 and provide further experimental detail. The references are designated by either a patent/publication number or the first author of a scientific journal publication. Full scientific journal publication references are provided below in alphabetical order according to first

35 author:

Albright, et al., J. Het. Chem. 2000, 37, 41-46;

Armstrong, et al., Tetrahedron Lett. 1994, 35, 3239-3242;

- Ball, et al., J. Heterocyclic Chem. 1990, 27, 279-286;
- Bell, et al., J. Med. Chem. 1998, 41, 2146-2163;
- Berg-Nielsen, et al., Acta Chem. Scand. B 1978, 32, 553-556;
- 5 DeVita, et al., Bioorg. & Med. Chem. Lett. 1995, 5, 1281-1286;
- Caprathe, et al., J. Med. Chem. 1991, 34, 2736-2746;
- Carling, et al., J. Med. Chem. 1993, 36, 3397-3408;
- Casimir, et al., J. Org. Chem. 2000, 65, 6487-6492;
- 10 Davis et al., Arch. Biochem. Biophys. 1963, 102, 48-51;
- Davis, et al., J. Med. Chem. 1972, 15, 325-327;
- Davis, et al., J. Het. Chem. 1980, 17, 1405-1408;
- El-Subbagh, et al., Arch. Pharm. Med. Chem. 1999, 332, 19-24;
- 15 Epszajn, et al, J. Chem. Soc. Perkin Trans. I 1985, 213-219;
- Flynn, et al., Biorg. & Med. Chem. Lett. 1991, 1, 309-312;
- Fujita, et al., Synth. 1988, 599-604;
- 20 Huang, et al., Synth. Commun. 1998, 28, 1197-1200;
- Itoh, et al., Chem. Pharm. Bull. 1986, 34, 1128-1147;
- Jackson, et al., J. Org. Chem. 1998, 63, 7875-7884;
- Jössang-Yanagida, et al., J. Het. Chem. 1978, 15, 249-251;
- 25 Kikelj, et al., J. Het. Chem. 1993, 30, 597-602;
- Kluge, et al., J. Heterocyclic Chem. 1996, 33, 1623-1626;
- Lardenois, et al., Synth. Commun. 1996, 26, 2305-2308;
- Lowe, et al., J. Med. Chem. 1994, 37, 3789-3811;
- McCord, et al., J. Het. Chem. 1981, 18, 1035-1039;
- 30 Morton, et al., Tetrahedron Letters 2000, 41, 3029-3033;
- Murakami, et al., J. Med. Chem. 1999, 42, 2621-2632;
- Parsons, et al., Biochem. Biophys. Res. Comm. 1983, 117, 108-113;
- Rabi-Barakay, et al., Tetrahedron 1994, 50, 10771-10782;
- 35 Robl, et al., Bioorg. & Med. Chem. Lett. 1994, 4, 1789-1794;
- Saari, et al., J. Med. Chem. 1992, 35, 3792-3802;

- Schoen, et al., J. Med. Chem. 1994, 37, 897-906;
 Sicker et al., Synth. 1985, 331-333;
 Sicker, et al., J. Het. Chem. 1994, 31, 809-812;
 Slade, et al., J. Med. Chem. 1985, 28, 1517-1521;
 5 Tamura, et al., Bioorg. & Med. Chem. Lett. 1999, 9, 2573-2578;
 Tietze, et al., Synth. 1991, 1118-1120;
 Turconi, et al., Bioorg. & Med. Chem. 1994, 2, 1375-1383;
 Van Niel, et al., Bioorg. & Med. Chem. Lett. 1995, 5,
 10 1421-1426;
 Watthey, et al., J. Med. Chem. 1985, 28, 1511-1516;
 Worley, et al., J. Org. Chem. 1975, 40, 1731-1734.

15 Since those skilled in the art recognize that the efficiency of a chemical reaction is often related to the degree of structural similarity between the substrates, and those in the literature procedure followed, the context of the references in the synthetic schemes is provided below for convenience.

20 Amines III and protected amines IV where X is CH₂, Y is a bond, Z is a benzene ring and R¹ is hydrogen may be prepared according to the routes and procedures described in Davis 1972; Tamura; Davis 1963; US 5849918; WO 9636596; US 5206235.

25 Intermediates leading to protected amines IV where X is CH₂, Y is a bond, Z is a benzene ring and R¹ is hydrogen may be prepared according to the routes and procedures described in WO 9743268.

30 Amines III and protected amines IV where X is CHR⁵, Y is a bond, Z is a benzene ring, R⁵ is not hydrogen and R¹ is hydrogen may be prepared according to the routes and procedures described in McCord; Davis 1980; Carling; WO 9314067.

35 Amines III and protected amines IV where X is CH₂, Y is a bond, Z is a benzene ring and R¹ is not hydrogen may be prepared according to the routes and procedures described in Davis 1980; Turconi.

Amines III and protected amines IV where X is CH_2CH_2 , Y is a bond and Z is a benzene ring may be prepared according to the routes and procedures described in US 5849918; EP 107095; US 4692522; Tamura; Jackson;
 5 Armstrong; Schoen; Robl; Watthey; Parsons; US 5206235.

Amines III and protected amines IV where X is CH_2CHR^5 , Y is a bond, Z is a benzene ring and R^5 is not hydrogen may be prepared according to the routes and procedures described in Lowe.

10 Amines III and protected amines IV where X is CHR^5O or CHR^5S , Y is a bond and Z is a benzene ring may be prepared according to the routes and procedures described in Robl; Slade; Itoh; US 5552397; US 4512988; DeVita; US 5206235.

15 Protected amines IV where X is CH_2CO , Y is a bond and Z is a benzene ring may be prepared according to the routes and procedures described in Ball; Van Niel; DeVita.

20 Amines III where X is O or S, Y is a bond and Z is a benzene ring may be prepared according to the routes and procedures described in Kluge; US 5206235; DeVita.

Intermediates leading to amines III where X is O or S, Y is a bond and Z is a benzene ring may be prepared according to the routes and procedures described in
 25 Tietze; Fujita; Worley; Sicker 1994; El-Subbagh; US 4755509; Kikelj; US 6017926.

Amines III and protected amines IV where X is CHR^5 or S, Y is CHR^6 and Z is a benzene ring may be prepared according to the routes and procedures described in US
 30 5545735; Rabi-Barakay; Flynn; Casimir.

Intermediates leading to amines III and protected amines IV where X is CHR^5 , Y is a bond and Z is a pyridine ring may be prepared according to the routes and procedures described in Caprathe; Berg-Nielsen; Huang.

35 Amines III and protected amines IV where X is CHR^5O CHR^5S , or CHR^5SO_2 , Y is a bond and Z is a pyridine ring

may be prepared according to the routes and procedures described in Morton; JP 2000-256318.

Amines III and protected amines IV where X is CH_2CHR^5 , Y is a bond and Z is a pyridine ring may be prepared according to the routes and procedures described in US 5789587; JP 2000-256318.

Intermediates leading to amines III and protected amines IV where X is CH_2CHR^5 , Y is a bond and Z is a pyridine ring may be prepared according to the routes and procedures described in Lardenois; Epsztajn; Huang; US 5719278; Jössang-Yanagida; Berg-Nielsen; Albright; Caprathe; WO 0100586; Bell.

Intermediates leading to amines III where X is O or S, Y is a bond and Z is a pyridine ring may be prepared according to the routes and procedures described in US 3749715; El-Subbagh; US 4755509; US 5652363; US 6017926; EP 416740; Sicker 1985; Kikelj; EP 160546.

Amines III and protected amines IV where X is CH_2CHR^5 , Y is a bond and Z is a thiophene ring may be prepared according to the routes and procedures described in US 5789587.

References to examples of the manipulation of R^2 in synthetic intermediates denoted @ include the following: III where X is CH_2 , Y is a bond and Z is a benzene ring: Parsons; EP 107095; US 4692522; US 5849918.

IV where X is CH_2 , Y is a bond and Z is a benzene ring: US 5594006.

IV where X is CH_2CH_2 , Y is a bond and Z is a benzene ring: Parsons; EP 107095; US 4692522; Robl; Murakami.

IV where X is CH_2O , Y is a bond and Z is a benzene ring: Robl; Murakami; Itoh.

IV where X is CH_2S , Y is a bond and Z is a benzene ring: Slade; Robl; Itoh.

IV where X is CH_2CO , Y is a bond and Z is a benzene ring: Ball; Van Niel.

IV where X is CH_2 , Y is CH_2 and Z is a benzene ring: US 5545735.

IV where X is CHR^5O , Y is a bond and Z is a pyridine ring: JP 2000-256318.

IV where X is CHR^5S , Y is a bond and Z is a pyridine ring: Morton; JP 2000-256318.

- 5 IV where X is S, Y is a bond and Z is a pyridine ring: US 4755509.

Unsaturated nitro compound in Scheme 24: Tamura.

Alpha halo lactam in Scheme 11: Lowe.

Alpha azido lactam in Scheme 11: JP 2000-256318.

- 10 Curtius precursor in Scheme 23: Kikelj.

The references above are incorporated herein by reference.

UTILITY & COMBINATIONS

15

A. UTILITIES

- The compounds of the present invention possess activity as inhibitors of the enzyme glycogen phosphorylase and therefore may be used in the treatment of diseases associated with glycogen phosphorylase activity. Via the inhibition of glycogen phosphorylase, the compounds of the present invention may preferably be employed to inhibit glycogenolysis, thereby interrupting or modulating hepatic glucose production.
- 20
- 25

- Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to, treating or delaying the progression or onset of diabetes (including Type I and Type II, impaired glucose tolerance, insulin resistance and diabetic complications, such as nephropathy, retinopathy and neuropathy), hyperglycemia, hyperinsulinemia, hypercholesterolemia, elevated blood levels of free fatty acids or glycerol, hyperlipidemia, dislipidemia, hypertriglyceridemia, obesity, delayed wound healing, atherosclerosis and hypertension.
- 30
- 35

Further, the compounds of the present invention can be used to treat or prevent infection in a mammal, e.g., bacterial, fungal, parasitic or viral infection.

In addition, the conditions, diseases, and maladies collectively referred to as "Syndrome X" or Metabolic Syndrome as detailed in Ford, et al., *J. Am. Med. Assoc.* **2002**, 287, 356-359 and Arbeeny, et al., *Curr. Med. Chem. - Imm., Endoc. & Metab. Agents* **2001**, 1, 1-24, may be treated employing the compounds of the invention.

B. COMBINATIONS

The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), e.g., an antidiabetic agent or other pharmaceutically active material.

The compounds of the present invention may employed in combination with other glycogen phosphorylase inhibitors or one or more other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents; anti-atherosclerotic agents; anti-ischemic agents; anti-infective agents; anti-cancer and cytotoxic agents; anti-hyperglycemic agents; lipid lowering agents; anti-hypertensive agents; anti-obesity agents and appetite suppressants.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include insulin and insulin analogs: LysPro insulin, inhaled formulations comprising insulin; glucagon-like peptides; sulfonylureas and analogs: chlorpropamide,

glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glyburide, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; alpha2-antagonists and imidazolines: midaglizole,
5 isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linoglriride, insulinotropin, exendin-4, BTS-67582, A-4166; thiazolidinediones: ciglitazone, pioglitazone, troglitazone, rosiglitazone; PPAR-gamma agonists; PPAR-alpha agonists; PPAR
10 alpha/gamma dual agonists; SGLT2 inhibitors; dipeptidyl peptidase-IV (DPP4) inhibitors; aldose reductase inhibitors; RXR agonists: JTT-501, MCC-555, MX-6054, DRF2593, GI-262570, KRP-297, LG100268; fatty acid oxidation inhibitors: clomoxir, etomoxir; α -glucosidase
15 inhibitors: precose, acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; beta-agonists: BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, TAK-667, AZ40140; phosphodiesterase inhibitors, both cAMP and cGMP type: sildenafil, L686398: L-386,398;
20 amylin antagonists: pramlintide, AC-137; lipoxygenase inhibitors: masoprocal; somatostatin analogs: BM-23014, seglitide, octreotide; glucagon antagonists: BAY 276-9955; insulin signaling agonists, insulin mimetics, PTP1B inhibitors: L-783281, TER17411, TER17529; gluconeogenesis
25 inhibitors: GP3034; somatostatin analogs and antagonists; antilipolytic agents: nicotinic acid, acipimox, WAG 994; glucose transport stimulating agents: BM-130795; glucose synthase kinase inhibitors: lithium chloride, CT98014, CT98023 and galanin receptor agonists.
30 Other suitable thiazolidinediones include Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Welcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645
35 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi).

Suitable PPAR alpha/gamma dual agonists include AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a
 5 Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma; Effect of PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998), and WO 01/21602, the disclosure of which is
 10 incorporated herein by reference, employing dosages as set out therein, which compounds designated as preferred are preferred for use herein.

Suitable alpha2 antagonists also include those disclosed in WO 00/59506, employing dosages as set out
 15 herein.

Suitable SGLT2 inhibitors include T-1095, phlorizin, WAY-123783 and those described in WO 01/27128.

Suitable DPP4 inhibitors include those disclosed in WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG),
 20 WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) as disclosed by Hughes et al, Biochemistry, 38 (36), 11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-
 25 tetrahydroisoquinoline-3-carboxylic acid (disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540, 2-cyanopyrrolidides and 4- cyanopyrrolidides, as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996)
 30 employing dosages as set out in the above references.

Suitable aldose reductase inhibitors include those disclosed in WO 99/26659.

Suitable meglitinides include nateglinide (Novartis) or KAD1229 (PF/Kissei).

35 Examples of glucagon-like peptide-1 (GLP-1) include GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as

disclosed in U.S. Patent No. 5,614,492 to Habener), as well as AC2993 (Amylen) and LY-315902 (Lilly).

Other anti-diabetic agents that can be used in combination with compounds of the invention include
 5 ergoset and D-chiroinositol.

Examples of suitable lipid lowering agents for use in combination with the compounds of the present invention include one or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors,
 10 fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na⁺/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile acid sequestrants, cholesterol ester transfer protein inhibitors (e.g., CP-
 15 529414 (Pfizer)) and/or nicotinic acid and derivatives thereof.

MTP inhibitors which may be employed as described above include those disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Patent No. 5,962,440.

The HMG CoA reductase inhibitors which may be employed in combination with one or more compounds of
 25 formula I include mevastatin and related compounds, as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds, as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds, such as disclosed in U.S. Patent No. 4,346,227,
 30 simvastatin and related compounds, as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin, as disclosed
 35 in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin, as disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, atavastatin

(Nissan/Sankyo's nisvastatin (NK-104)), as disclosed in U.S. Patent No. 5,011,930, visastatin (Shionogi-Astra/Zeneca (ZD-4522)), as disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives, as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof, as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives, as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes, such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin), as disclosed in European Patent Application No. 0142146 A2, and quinoline and pyridine derivatives, as disclosed in U.S. Patent No. 5,506,219 and 5,691,322.

Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin and ZD-4522.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase, such as those disclosed in GB 2205837, are suitable for use in combination with the compounds of the present invention.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α -phosphonosulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)phosphonates, as well as other known squalene

synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

5 In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-
10 PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah,
15 Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

 The fibric acid derivatives which may be employed in combination with one or more compounds of formula I include fenofibrate, gemfibrozil, clofibrate,
20 bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds, as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants, such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®,
25 Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814
30 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives, such as
35 disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes, such

as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

The ACAT inhibitor which may be employed in combination with one or more compounds of formula I
5 include those disclosed in Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85;
10 "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a
15 bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al,
20 Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Manfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of
25 acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-
30 phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd).

The hypolipidemic agent may be an upregulator of LD2
35 receptor activity, such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

Examples of suitable cholesterol absorption inhibitor for use in combination with the compounds of the invention include SCH48461 (Schering-Plough), as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

Examples of suitable ileal Na⁺/bile acid cotransporter inhibitors for use in combination with the compounds of the invention include compounds as disclosed in Drugs of the Future, 24, 425-430 (1999).

The lipoxygenase inhibitors which may be employed in combination with one or more compounds of formula I include 15-lipoxygenase (15-LO) inhibitors, such as benzimidazole derivatives, as disclosed in WO 97/12615, 15-LO inhibitors, as disclosed in WO 97/12613, isothiazolones, as disclosed in WO 96/38144, and 15-LO inhibitors, as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1

receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g.,
 5 compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

10 Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta drug and/or an anorectic agent.

The beta 3 adrenergic agonists which may be
 15 optionally employed in combination with compounds of the present invention include AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer,) or other known beta 3 agonists, as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064,
 20 with AJ9677, L750,355 and CP331648 being preferred.

Examples of lipase inhibitors which may be optionally employed in combination with compounds of the present invention include orlistat or ATL-962 (Alizyme), with orlistat being preferred.

25 The serotonin (and dopamine) reuptake inhibitor which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

30 Examples of thyroid receptor beta compounds which may be optionally employed in combination with compounds of the present invention include thyroid receptor ligands, such as those disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio) and GB98/284425 (KaroBio), with
 35 compounds of the KaroBio applications being preferred.

The anorectic agent which may be optionally employed in combination with compounds of the present invention

include dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

Other compounds that can be used in combination with the compounds of the present invention include CCK
5 receptor agonists (e.g., SR-27897B); galanin receptor antagonists; MCR-4 antagonists (e.g., HP-228); leptin or mimentics; 11-beta-hydroxysteroid dehydrogenase type-1 inhibitors; urocortin mimetics, CRF antagonists, and CRF binding proteins (e.g., RU-486, urocortin).

10 The aforementioned patents and patent applications are incorporated herein by reference.

The above other therapeutic agents, when employed in combination with the compounds of the present invention may be used, for example, in those amounts indicated in
15 the Physician's Desk Reference, as in the patents set out above or as otherwise determined by one of ordinary skill in the art.

The compounds of the formula I can be administered for any of the uses described herein by any suitable
20 means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous
25 or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing
30 non-toxic, pharmaceutically acceptable vehicles or diluents.

In carrying out the method of the invention for treating diabetes and related diseases, a pharmaceutical composition will be employed containing the compounds of
35 formula I, with or without other antidiabetic agent(s) and/or antihyperlipidemic agent(s) and/or other type therapeutic agents in association with a pharmaceutical

vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration, such as pharmaceutically acceptable carriers, excipients, binders and the like. The compounds can be administered to mammalian patient, including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, beads, granules or powders. Typical solid formulations will contain from about 1 to about 1000 mg of a compound of formula I. The dose for adults is preferably between 1 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

Glycogen phosphorylase inhibitor activity of the compounds of the invention may be determined by use of an assay system as set out below.

Assay for Glycogen Phosphorylase Activity

The utility of the compounds of the invention for use in the treatment of diabetes and the other components of Syndrome X and in ischemia may be demonstrated in assays for glycogen phosphorylase inhibition in vitro (US 6,107,329), effects on blood sugar and insulin in vivo (US 6,107,329), and effects on ischemic tissue damage in vitro (US 6,107,329), and for effects on weight and food intake in vivo (WO 00/47206).

The following working Examples serve to better illustrate, but not limit, some of the preferred embodiments of the present invention. Examples 56 to 62 are embodiments of the present invention. Examples 1 to 5 55 illustrate the preparation of compounds of formulas Ia and Ib.

General

10 Reverse phase preparative HPLC separation employed an octadecyl sulfate (C-18) column eluting with a solvent gradient of solvents A and B, starting with 20% or more of solvent B and finishing with 100% of solvent B. Solvent A was 10% methanol in water, and solvent B was 15 90% methanol in water. In certain cases both solvents A and B contained 0.1% of trifluoroacetic acid, as noted.

Preparation of Resin Bound Activated Ester

20 To a suspension of triphenylphosphine (3.9 g) and 5-chloroindole-2-carboxylic acid (2.9 g) in tetrahydrofuran (100 mL) at room temperature, was added trichloroacetonitrile (2.2 g). The resulting yellow mixture was shaken for 2 h before diisopropylethylamine 25 (2.0 g) and polymer-supported tetrafluorophenol (5.0 g, J. M. Salvino, et al., J. Combinatorial Chem. 2000, 2, in press) were added, followed by additional tetrahydrofuran (100 mL). After shaking for 5 h, the solution was drained from the now light brown mixture, and the resin 30 was washed sequentially with N,N-dimethylformamide (50 mL twice), tetrahydrofuran (50 mL twice), and dichloromethane (50 mL twice). Mixed with the resin was a small amount of a yellow, insoluble solid, which was removed by separation in dichloromethane, in which the 35 insoluble solid sank and the resin floated. Resin bound activated ester (5.9 g) was obtained after drying under vacuum. Loading was determined to be 1.0 mmol/g by

measurement of the amount of 5-chloro-N-isopropyl-indolecarboxamide obtained after reaction with a large excess isopropylamine in dichloromethane.

5 Resin Capture Procedure

 A mixture of amine (about 0.04 mmol) and the resin bound activated ester prepared above (about 0.05 mmol, always in excess) in tetrahydrofuran (1-2 mL) was shaken
10 room temperature for 1-2 days. The mixture was filtered and the resin was rinsed with tetrahydrofuran (1 mL). The combined filtrate and rinses were evaporated under vacuum and analyzed by HPLC/MS. Starting amines used were free bases unless otherwise noted. In cases where
15 an amine salt was used, a scavenger base was also present, as noted.

Carbodiimide Mediated Amide Bond Formation Procedure

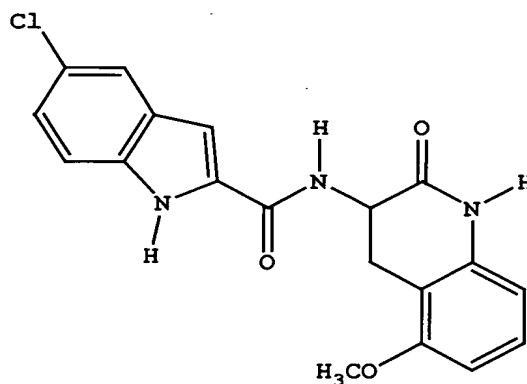
20 A mixture of amine (0.04 - 0.23 mmol), N,N-dimethylformamide (0.8 mL), 5-chloroindole-2-carboxylic acid (1-2 equiv), 1-hydroxy-7-azabenzotriazole (1-2 equiv), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.5-2.0 equiv) was
25 stirred at room temperature. The starting amines were free bases unless otherwise noted. In cases where an amine salt was used, a scavenger base, generally triethylamine (1-2 equiv), was also present. After 16 h, 1.0 M aqueous sodium bicarbonate (0.5 mL) was added to
30 hydrolyze any remaining activated ester. Water (2 mL) was added 1 day later, and the resulting precipitated mixture was centrifuged. The supernatant was removed, and the precipitate was washed by resuspension in water, centrifugation, and supernatant removal. In cases where
35 an additional chemical step was required, such as ester hydrolysis, this crude amide product was used without further purification. In cases where the amide was the

final product, further purification was performed as follows. A. The crude amide was stirred at room temperature in N,N-dimethylformamide (0.5 mL), then diluted with methanol (1 mL) and water (0.1 mL). B. The supernatant was injected onto reverse phase preparative HPLC using trifluoroacetic acid containing solvents to isolate pure amide product. Steps A and B were repeated with any remaining precipitate until either the precipitate contained no amide product or the precipitate was pure amide product.

Ester Hydrolysis Procedure

Ester (0.05 - 0.10 mmol), was dissolved in a mixture of ethanol (1 mL) and 1.0 M aqueous sodium hydroxide (0.5 mL). After stirring at room temperature for 6 h, the mixture was acidified to pH 1-2 by addition of trifluoroacetic acid (0.1 mL), and the product acid was purified by reverse phase preparative HPLC using trifluoroacetic acid containing solvents.

**Example 1
racemate**



Example 1**3-(5-chloroindole-2-carbonylamino)-5-methoxy-3,4-dihydrocarbostyryl**

5

Sodium metal (1.15 g) was dissolved in absolute ethanol (500 mL), and to the resulting solution was added diethyl 2-acetylaminomalonate (9.1 g). After 15 min at room temperature, a solution of 2-methoxy-6-nitrobenzyl bromide (J. Med. Chem. 1977, 20, 190-196) (8.6 g) in tetrahydrofuran (25 mL) was added over 2 min. After 16 h stirring at room temperature the mixture was evaporated. The residue was dissolved in a mixture of ethyl acetate and water. The ethyl acetate layer was separated and washed sequentially with water and brine before drying over anhydrous sodium sulfate. Evaporation was followed by silica gel chromatography eluting initially with dichloromethane, followed by ethyl acetate, to obtain diethyl 2-acetyl-amino-2-(2-methoxy-6-nitrobenzyl)malonate (10.8 g).

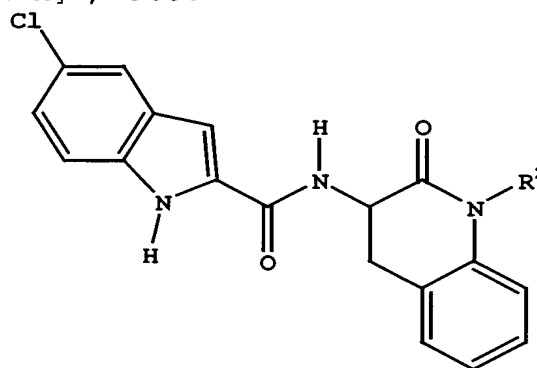
A mixture of diethyl 2-acetyl-amino-2-(2-methoxy-6-nitrobenzyl)malonate (10.5 g), 10% palladium on carbon (1.0 g), and absolute ethanol (200 mL) was shaken under a hydrogen atmosphere at 60 psi for 45 min. Addition of more 10% palladium on carbon (1.0 g) and further hydrogenation for 20 min was followed by filtration and evaporation of the filtrate. The residue was triturated with 20% methanol in toluene, and the solid was filtered to obtain 3-acetamido-amino-3-carboethoxy-5-methoxy-3,4-dihydrocarbostyryl (7.5 g, mp 258-259 °C).

A mixture of 3-acetamido-amino-3-carboethoxy-5-methoxy-3,4-dihydrocarbostyryl (5.7 g) and 6 M aqueous hydrochloric acid (75 mL) was refluxed for 6 h. This mixture was evaporated to a solid which was triturated with acetonitrile. Filtration provided 3-amino-5-methoxy-3,4-dihydrocarbostyryl hydrochloride (3.8 g, mp 301-302 °C with decomp.) as gray crystals. The free

base, 3-amino-5-methoxy-3,4-dihydrocarbostyryl, was prepared by ion exchange on an SCX column (United Chemical Technologies, CLEAN-UP Extraction Column, sorbent CUBCX1HL, Synthesis 1997, 553-558) by loading in
 5 methanol and eluting with methanol, followed by 2 M methanolic ammonia. The ammonia containing eluant was evaporated to provide 3-amino-5-methoxy-3,4-dihydrocarbostyryl.

The title compound was prepared by reaction of the
 10 resin bound activated ester with 3-amino-5-methoxy-3,4-dihydrocarbostyryl according to Resin Capture Procedure. HPLC/MS $[M+H]^+$, 370; $[M-H]^-$, 368.

Examples 2-18
 see table



Example	R ²	Stereochemistry
2	H	racemate
3, 5	H	R
4, 6	H	S
7	CH ₂ CO ₂ CH ₃	R
8	CH ₂ CO ₂ CH ₃	S
9	CH ₂ CO ₂ H	R
10	CH ₂ CO ₂ H	S
11	CH ₂ CH ₂ OH	S
12	CH ₂ CONH ₂	R
13	CH ₂ CONH ₂	S
14	OCH ₃	R
15	OCH ₃	S
16	CH ₂ CH=CH ₂	S
17	CH ₂ CN	S
18	CH ₂ CN	R

Example 2**3-(5-chloroindole-2-carboxylamino)-3,4-dihydrocarbostyryl**

5 The title compound was prepared by reaction of the resin bound activated ester with 3-amino-3,4-dihydrocarbostyryl (Arch. Biochem. Biophys. 1963, 102, 48-51) according to Resin Capture Procedure. HPLC/MS
10 $[M+H]^+$, 340; $[M-H]^-$, 338.

Homochiral compounds of the title compound from Example 2 were produced in the following Examples 3 and 4.

15

Example 3**(R)-3-(5-chloroindole-2-carboxylamino)-3,4-dihydrocarbostyryl**

20

Resolution of 3-amino-3,4-dihydrocarbostyryl (Arch. Biochem. Biophys. 1963, 102, 48-51) was performed by separating a racemic mixture of 3-amino-3,4-dihydrocarbostyryl into its component (R) and (S) enantiomers by chiral normal phase preparative HPLC (Chiralcel AS column, 25% ethanol in hexane). Analysis was by chiral normal phase analytical HPLC (Chiralcel AS column, 30% ethanol in hexane, S isomer elutes before R isomer).

30 The title compound was prepared by reaction of the resin bound activated ester with (R)-3-amino-3,4-dihydrocarbostyryl according to the Resin Capture Procedure. HPLC/MS $[M+H]^+$, 340; $[M-H]^-$, 338.

Example 4

(S)-3-(5-chloroindole-2-carboxylamino)-3,4-
dihydrocarbostyryl

5

The title compound was prepared by reaction of the resin bound activated ester with (S)-3-amino-3,4-dihydrocarbostyryl from Example 3 according to the Resin Capture Procedure.

10 HPLC/MS $[M+H]^+$, 340; $[M-H]^-$, 338.

Example 5

(R)-3-(5-chloroindole-2-carboxylamino)-3,4-
dihydrocarbostyryl

15

To a suspension of racemic 3-amino-3,4-dihydrocarbostyryl hydrochloride (300 mg) in acetonitrile (20 mL) at room temperature was added aqueous sodium bicarbonate (378 mg in 5 mL of water) followed by di-*t*-butyl dicarbonate (425 mg). After stirring for 3 h, the solvent was removed under vacuum, and the residue was dissolved in ethyl acetate. This was washed sequentially with 1 M aqueous sodium hydroxide (60 mL) and brine (60 mL) before drying over anhydrous sodium sulfate and evaporation under vacuum to provide 3-*t*-butyloxycarbonylamino-3,4-dihydrocarbostyryl (413 mg), which was separated into its homochiral component enantiomers (R) and (S) 3-*t*-butyloxycarbonylamino-3,4-dihydrocarbostyryl by chiral normal phase preparative HPLC (Chiralcel AD column, 10% isopropanol in hexane). Analysis was by chiral normal phase analytical HPLC (Chiralcel AD column, 10% isopropanol in hexane, R isomer elutes before S isomer).

35 (R)-3-*t*-butyloxycarbonylamino-3,4-dihydrocarbostyryl (178 mg) was dissolved in 4 M hydrogen chloride in 1,4-dioxane solution (10 mL) at 0°C. After 1 h the solution

was slowly warmed to room temperature over 2 h. The solvent was evaporated under vacuum, and the residue was twice taken up in toluene (10 mL) and evaporated under vacuum to provide (R)-3-amino-3,4-dihydrocarbostyryl hydrochloride, a white solid (132 mg).

(R)-3-amino-3,4-dihydrocarbostyryl hydrochloride (132 mg) was treated with resin bound activated ester according to the Resin Capture Procedure, but on 14 times the standard scale and with diisopropylethylamine (1 mL) present. Crude product was purified by reverse phase preparative HPLC to provide 193 mg of the title compound. HPLC/MS $[M+H]^+$, 340.

Alternatively, (R)-3-amino-3,4-dihydrocarbostyryl hydrochloride (95 mg) was added to a mixture of tetrahydrofuran (10 mL), 5-chloroindole-2-carboxylic acid (103 mg), 1-hydroxy-7-azabenzotriazole (85 mg), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (120 mg) at room temperature. Diisopropylethylamine (186 mg) was added, and the resulting yellow suspension was stirred for 2 h, during which a solution formed. The solution was diluted with ethyl acetate (50 mL) and washed sequentially with 1.0 M aqueous hydrochloric acid (25 mL), 1.0 M aqueous sodium hydroxide (25 mL), and brine (25 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum. The resulting solid crude product was triturated with diethyl ether (5 mL twice), then 50% methanol in diethyl ether (5 mL twice). Drying under vacuum provided pure title compound (132 mg).

Example 6

(S)-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl

The title compound was prepared from (S)-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl (prepared in Example 5) by the procedures described for the

preparation of (R)-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (Example 5) from (R)-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl. HPLC/MS $[M+H]^+$, 340; $[M+Na]^+$, 362.

5

Example 7

(R)-1-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl

10

(R)-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl (26 mg), as prepared in Example 5, was dissolved in tetrahydrofuran (5 mL) at room temperature under argon. To the stirring solution was added methyl bromoacetate (31 mg), followed by sodium methoxide (26 mg). The resulting suspension was stirred for 30 min before dilution with ethyl acetate (25 mL) and water (25 mL). The organic phase was separated, washed with water (25 mL), and dried over anhydrous sodium sulfate. After solvent evaporation under vacuum, the crude product was purified by reverse phase preparative HPLC to provide (R)-3-t-butyloxycarbonylamino-1-carbomethoxymethyl-3,4-dihydrocarbostyryl (24 mg).

(R)-3-t-butyloxycarbonylamino-1-carbomethoxymethyl-3,4-dihydrocarbostyryl (20 mg) was dissolved in 4 M hydrogen chloride in 1,4-dioxane solution (5 mL) at room temperature. After 1 h the solvent was evaporated under vacuum, and the residue was twice taken up in toluene (10 mL) and evaporated under vacuum to provide (R)-3-amino-1-carbomethoxymethyl-3,4-dihydrocarbostyryl hydrochloride, a white solid (21 mg).

(R)-3-amino-1-carbomethoxymethyl-3,4-dihydrocarbostyryl hydrochloride (21 mg) was treated with resin bound activated ester according to Resin Capture Procedure with diisopropylethylamine (1 mL) present. The resin was rinsed with tetrahydrofuran, N,N-dimethylformamide, and dichloromethane. The combined

filtrate and rinses were evaporated under vacuum, and the residue was purified by reverse phase preparative HPLC to provide the title compound (13 mg). HPLC/MS $[M+H]^+$, 412; $[M+Na]^+$, 434.

5 Alternatively, (R)-3-amino-1-carbomethoxymethyl-3,4-dihydrocarbostyryl hydrochloride (19 mg) was added to a mixture of tetrahydrofuran (10 mL), 5-chloroindole-2-carboxylic acid (15 mg), 1-hydroxy-7-azabenzotriazole (12 mg), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
10 hydrochloride (16 mg) at room temperature. Diisopropylethylamine (19 mg) was added, and the resulting yellow suspension was stirred under argon for 16 h, during which a solution formed. The solution was diluted with ethyl acetate (50 mL) and washed
15 sequentially with 1.0 M aqueous hydrochloric acid (25 mL twice), 1.0 M aqueous sodium hydroxide (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and evaporated under vacuum. One half of the residue was purified by reverse phase preparative HPLC to provide the
20 title compound (7.6 mg).

Example 8

25 (S)-1-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl

30 The title compound was prepared from (S)-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl (prepared in Example 5) by the procedures described for the preparation of (R)-1-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (Example 7) from (R)-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl. HPLC/MS $[M+H]^+$, 412.

Example 9

(R)-1-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-
3,4-dihydrocarbostyryl

5

(R)-1-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (Example 7) (13 mg) was dissolved in a 2:2:1 mixture of tetrahydrofuran, methanol, and water (5 mL). Lithium hydroxide monohydrate (3 mg) was added, and the resulting mixture was stirred at room temperature for 2 h. Addition of 1.0 M aqueous hydrochloric acid (10 mL) was followed by extraction with ethyl acetate (20 mL twice). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum to provide the title compound (12 mg). HPLC/MS [M+H]⁺, 398.

10

15

Example 10

20

(S)-1-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-
3,4-dihydrocarbostyryl

25

30

The title compound was prepared from (S)-1-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (Example 8) by the procedures described for the preparation of (R)-1-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (Example 9) from (R)-1-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl. HPLC/MS [M+H]⁺, 398.

Example 11**(S)-1-(2-hydroxyethyl)-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl**

5

A mixture of (S)-1-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (Example 10) (6 mg) in 1.0 M borane in tetrahydrofuran solution (2 mL) under argon was stirred at 35 °C for 3 h. After cooling to room temperature, 1.0 M aqueous hydrochloric acid (10 mL) and ethyl acetate (10 mL) were added. This mixture was stirred for 3 h before the layers were separated. The organic phase was washed with water (10 mL three times) and evaporated under vacuum. The residue was chromatographed on reverse phase preparative HPLC to isolate the title compound (1.1 mg) and the over-reduction product (S)-1-(2-hydroxyethyl)-3-(5-chloroindole-2-carbonylamino)-1,2,3,4-tetrahydroquinoline (0.9 mg). Title compound HPLC/MS [M+H]⁺, 384.

20

Example 12**(R)-1-aminocarbonylmethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl**

25

(R)-1-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (Example 7) (5.6 mg) was dissolved in a mixture of tetrahydrofuran (2 mL) and 2 M ammonia in methanol solution (2 mL). After stirring for 16 h at room temperature, the solvent was evaporated under vacuum and the residue was coevaporated with toluene (5 mL twice) under vacuum. Purification by reverse phase preparative HPLC provided the title compound (3.4 mg). HPLC/MS [M+H]⁺, 397; HPLC/MS [M+H-NH₃]⁺, 380.

35

Example 13**(S)-1-aminocarbonylmethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl**

5

(S)-1-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (Example 8) (5 mg) was dissolved in a mixture of tetrahydrofuran (1 mL) and 2 M ammonia in methanol solution (2 mL). After stirring for 16 h at room temperature, the solvent was evaporated and the residue was coevaporated with methanol (3 mL twice) under vacuum. Purification by reverse phase preparative HPLC provided the title compound (2.2 mg). HPLC/MS [M+H]⁺, 397.

15

Example 14**(R)-3-(5-chloroindole-2-carbonylamino)-1-methyl-3,4-dihydrocarbostyryl**

20

(R)-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl (prepared in Example 5, 30 mg) was dissolved in tetrahydrofuran (5 mL) at room temperature under argon. To the stirring solution was added methyl iodide (32 mg), followed by sodium methoxide (7.5 mg). The resulting suspension was stirred for 30 min before dilution with ethyl acetate (25 mL) and water (25 mL). The organic phase was separated, washed with water (25 mL), and dried over anhydrous sodium sulfate. After solvent evaporation under vacuum, the crude product was purified by reverse phase preparative HPLC to provide (R)-3-t-butyloxycarbonylamino-1-methyl-3,4-dihydrocarbostyryl (24 mg).

(R)-3-t-butyloxycarbonylamino-1-methyl-3,4-dihydrocarbostyryl (20 mg) was dissolved in 4 M hydrogen chloride in 1,4-dioxane solution (5 mL) at room temperature. After 1 h the solvent was evaporated under

vacuum, and the residue was twice taken up in toluene (5 mL) and evaporated under vacuum to provide (R)-3-amino-1-methyl-3,4-dihydrocarbostyryl hydrochloride (25 mg).

(R)-3-amino-1-methyl-3,4-dihydrocarbostyryl
5 hydrochloride (25 mg) was treated with resin bound activated ester according to the Resin Capture Procedure with diisopropylethylamine (1 mL) present. The resin was rinsed with tetrahydrofuran, N,N-dimethylformamide, and dichloromethane. The combined filtrate and rinses were
10 evaporated under vacuum, and the residue was purified by reverse phase preparative HPLC to provide the title compound (13 mg). HPLC/MS $[M+H]^+$, 354.

Example 15

15

(S)-3-(5-chloroindole-2-carbonylamino)-1-methyl-3,4-
dihydrocarbostyryl

The title compound was prepared from (S)-3-t-
20 butyloxycarbonylamino-3,4-dihydrocarbostyryl (prepared in Example 5) by the procedures described for the preparation of (R)-3-(5-chloroindole-2-carbonylamino)-1-methyl-3,4-dihydrocarbostyryl (Example 14) from (R)-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl. HPLC/MS
25 $[M+H]^+$, 354.

Example 16

30

(S)-1-allyl-3-(5-chloroindole-2-carbonylamino)-3,4-
dihydrocarbostyryl

(S)-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl
(prepared in Example 5, 30 mg) was dissolved in tetrahydrofuran (5 mL) at room temperature under argon.
35 To the stirring solution was added sodium methoxide (20 mg), followed by allyl bromide (55 mg). The resulting suspension was stirred for 16 h before dilution with

ethyl acetate (20 mL) and water (20 mL). The organic phase was separated and dried over anhydrous sodium sulfate. After solvent evaporation under vacuum, the crude product was purified by reverse phase preparative HPLC to provide (S)-1-allyl-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl (10 mg).

(S)-1-allyl-3-t-butyloxycarbonylamino-3,4-dihydrocarbostyryl (9.7 mg) was dissolved in 4 M hydrogen chloride in 1,4-dioxane solution (2 mL) at room temperature, and a white precipitate soon formed. After 30 min the solvent was evaporated under vacuum, and the residue was twice taken up in toluene (5 mL) and evaporated to provide (S)-1-allyl-3-amino-3,4-dihydrocarbostyryl hydrochloride (7.6 mg).

(S)-1-allyl-3-amino-3,4-dihydrocarbostyryl hydrochloride (7.6 mg) was added to a mixture of tetrahydrofuran (4 mL), 5-chloroindole-2-carboxylic acid (6.9 mg), 1-hydroxy-7-azabenzotriazole (5.5 mg), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (7.7 mg) at room temperature. Diisopropylethylamine (12 mg) was added, and the resulting yellow suspension was stirred under argon for 16 h, during which a solution formed. The solution was evaporated under vacuum and the residue was directly purified by reverse phase preparative HPLC to provide the title compound (6.5 mg). HPLC/MS $[M+H]^+$, 380; HPLC/MS $[M+Na]^+$, 402.

Example 17

(S)-3-(5-chloroindole-2-carbonylamino)-1-cyanomethyl-3,4-dihydrocarbostyryl

(S)-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (Example 4, 13.4 mg) was dissolved in tetrahydrofuran (5 mL) at room temperature under argon with stirring. After cooling to 0°C, sodium methoxide

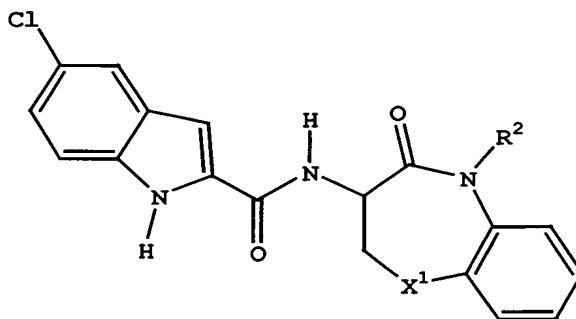
(4.3 mg) was added, followed 2 h later by bromoacetonitrile (7.2 mg). This was warmed to room temperature over 2 h, and 2 h later water (15 mL), 1.0 M aqueous hydrochloric acid (1 mL), and ethyl acetate (20 mL) were added. The organic phase was separated, washed with brine, and dried over anhydrous sodium sulfate. After solvent evaporation under vacuum, the crude product was purified by reverse phase preparative HPLC to provide the title compound (4 mg). HPLC/MS $[M+H]^+$, 379; HPLC/MS $[M+Na]^+$, 401.

Example 18

(R)-3-(5-chloroindole-2-carboxylamino)-1-cyanomethyl-3,4-dihydrocarbostyryl

The title compound was prepared from (R)-3-(5-chloroindole-2-carboxylamino)-3,4-dihydrocarbostyryl (Example 3) by the procedures described for the preparation of (S)-3-(5-chloroindole-2-carboxylamino)-1-cyanomethyl-3,4-dihydrocarbostyryl (Example 17) from (S)-3-(5-chloroindole-2-carboxylamino)-3,4-dihydrocarbostyryl. HPLC/MS $[M+H]^+$, 379.

Examples 19-21 and 24-31
see table



Example	X ¹	R ²	Stereochemistry
19	CH ₂	H	racemate
20	O	H	S
21	O	H	R
24	S	H	racemate
25	SO ₂	H	racemate
26	S	H	S
27	CH ₂	CH ₂ CO ₂ H	S
28	CH ₂	CH ₂ CO ₂ H	R
29	S	CH ₂ CO ₂ H	racemate
30	SO ₂	CH ₂ CO ₂ H	racemate
31	O	CH ₂ CO ₂ H	S

Example 19

5 3-(5-chloroindole-2-carboxylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

The title compound was prepared according to the Carbodiimide Mediated Amide Bond Formation Procedure from 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (amine prepared in Schoen, et al., J. Med. Chem. 1994, 37, 897-906). HPLC/MS [M+H]⁺, 354.

Example 20

15 (S)-3-(5-chloroindole-2-carboxylamino)-2,3-dihydro-1,5-benzoxazepin-4(5H)-one

The title compound was prepared according to the Carbodiimide Mediated Amide Bond Formation Procedure from (S)-3-amino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one trifluoroacetic acid salt (amine hydrochloride salt prepared in Itoh, et al., Chem. Pharm. Bull. 1986, 34, 1128-1147). HPLC/MS [M+H]⁺, 356.

Alternatively, to a mixture of (S)-3-amino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride salt (54 mg) (prepared in Itoh, et al., Chem. Pharm. Bull. 1986,

34, 1128-1147), tetrahydrofuran (10 mL), 5-chloroindole-2-carboxylic acid (39 mg), 1-hydroxy-7-azabenzotriazole (31 mg), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (57 mg) stirring at room temperature under argon was added diisopropylethylamine (65 mg). The resulting yellow suspension was stirred for 30 min, during which a solution formed. After evaporation under vacuum, the residue was redissolved in ethyl acetate (50 mL) and the resulting solution was washed sequentially with 1.0 M aqueous hydrochloric acid (25 mL), 1.0 M aqueous sodium hydroxide (25 mL), water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum. The resulting solid crude product was triturated with diethyl ether (20 mL three times), followed by drying under vacuum to provide the title compound (63 mg).

Example 21

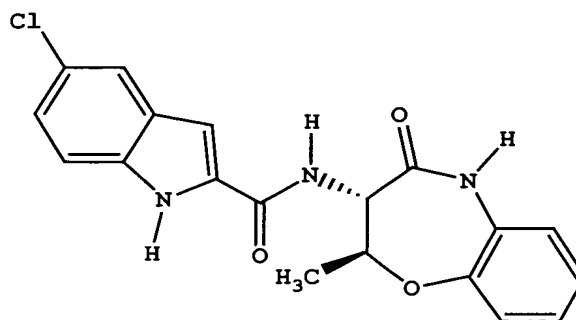
(R)-3-(5-chloroindole-2-carboxylamino)-2,3-dihydro-1,5-benzoxazepin-4(5H)-one

(R)-3-amino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride salt was prepared from N-t-butyloxycarbonyl-D-serine by the procedures described in Itoh, et al., Chem. Pharm. Bull. 1986, 34, 1128-1147 for the preparation of (S)-3-amino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride salt from N-t-butyloxycarbonyl-L-serine.

The title compound was prepared from (R)-3-amino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride salt by the procedures described for the preparation of (S)-3-(5-chloroindole-2-carboxylamino)-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (Example 20) from (S)-3-amino-2,3-

dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride salt.
HPLC/MS $[M+H]^+$, 356.

Example 22



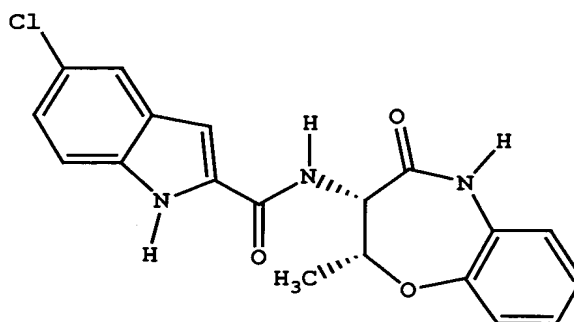
Example 22

(2S,3S)-3-(5-chloroindole-2-carbonylamino)-2-methyl-2,3-
dihydro-1,5-benzoxazepin-4(5H)-one

(2S,3S)-3-amino-2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one trifluoroacetate salt was prepared from (2S,3S)-3-t-butyloxycarbonylamino-2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (Robl, et al., Bioorg. & Med. Chem. Lett. 1994, 4, 1789-1794) by treatment with a solution of trifluoroacetic acid - dichloromethane - tetrahydrofuran (1:10:10) at room temperature, followed by solvent evaporation and coevaporation with tetrahydrofuran under vacuum.

The title compound was prepared from (2S,3S)-3-amino-2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one trifluoroacetate salt according to the Carbodiimide Mediated Amide Bond Formation Procedure with the following modifications: the reaction solvent was N,N-dimethylformamide - tetrahydrofuran (1:1), the scavenger base was diisopropylethylamine, no attempt was made to hydrolyze any residual activated ester, no attempt was made to precipitate desired product, and the product was

purified directly by reverse phase preparative HPLC.
HPLC/MS $[M+H]^+$, 370.

Example 23**Example 23**

(2S,3R)-3-(5-chloroindole-2-carbonylamino)-2-methyl-2,3-
dihydro-1,5-benzoxazepin-4(5H)-one

(2S,3R)-3-amino-2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one trifluoroacetate salt was prepared from (2S,3R)-3-t-butyloxycarbonylamino-2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (Robl, et al., Bioorg. & Med. Chem. Lett. 1994, 4, 1789-1794) by treatment with a solution of trifluoroacetic acid - dichloromethane - tetrahydrofuran (1:10:10) at room temperature, followed by solvent evaporation and coevaporation with tetrahydrofuran under vacuum.

The title compound was prepared from (2S,3R)-3-amino-2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one trifluoroacetate salt by the procedures described for the preparation of (2S,3S)-3-(5-chloroindole-2-carbonylamino)-2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one (Example 22) from (2S,3S)-3-amino-2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5H)-one trifluoroacetate salt. HPLC/MS $[M+H]^+$, 370.

Example 24**3-(5-chloroindole-2-carboxylamino)-2,3-dihydro-1,5-benzthiazepin-4(5H)-one**

5

3-Amino-2,3-dihydro-1,5-benzthiazepin-4(5H)-one trifluoroacetate salt was prepared from 3-t-butyloxycarbonylamino-2,3-dihydro-1,5-benzthiazepin-4(5H)-one (US 4512988) by treatment with trifluoroacetic acid in dichloromethane at room temperature, followed by solvent evaporation under vacuum.

The title compound was prepared from 3-amino-2,3-dihydro-1,5-benzthiazepin-4(5H)-one trifluoroacetate salt according to the Carbodiimide Mediated Amide Bond Formation Procedure. HPLC/MS $[M+H]^+$, 372.

15

Example 25**3-(5-chloroindole-2-carboxylamino)-2,3-dihydro-1,5-benzthiazepin-4(5H)-one S,S-dioxide**

20

To a solution of 3-(5-chloroindole-2-carboxylamino)-2,3-dihydro-1,5-benzthiazepin-4(5H)-one (Example 24) (5.6 mg) in tetrahydrofuran (2 mL) was added 60% 3-chloroperoxybenzoic acid (5.2 mg gross). After stirring at room temperature for 30 min, the mixture was directly injected onto reverse phase preparative HPLC, which separated the two sulfoxides from the title compound (2.5 mg). Further oxidation of the sulfoxides with 3-chloroperoxybenzoic acid in dichloromethane, followed by solvent evaporation under vacuum and reverse phase preparative HPLC provided title compound (1.0 mg). HPLC/MS $[M+H]^+$, 404.

30

Example 26

(S)-3-(5-chloroindole-2-carboxylamino)-2,3-dihydro-1,5-benzthiazepin-4(5H)-one

- 5 The title compound was prepared according to the Carbodiimide Mediated Amide Bond Formation Procedure from (S)-3-amino-2,3-dihydro-1,5-benzthiazepin-4(5H)-one trifluoroacetic acid salt (amine free base prepared in Slade, et al., J. Med. Chem. 1985, 28, 1517-1521).
- 10 HPLC/MS [M+H]⁺, 372.

Example 27

(S)-1-carboxymethyl-3-(5-chloroindole-2-carboxylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

- 15 The title compound was prepared in two steps according to the Carbodiimide Mediated Amide Bond Formation Procedure followed by the Ester Hydrolysis Procedure from (S)-1-carboethoxymethyl-3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one L-tartaric acid salt (amine L-tartaric acid salt prepared in Watthey, et al., J. Med. Chem. 1985, 28, 1511-1516). HPLC/MS [M+H]⁺, 412.

25 **Example 28**

(R)-1-carboxymethyl-3-(5-chloroindole-2-carboxylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

- 30 The title compound was prepared in two steps according to the Carbodiimide Mediated Amide Bond Formation Procedure followed by the Ester Hydrolysis Procedure from (R)-1-carboethoxymethyl-3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one D-tartaric acid salt
- 35 ((R)-amine D-tartaric acid salt prepared analogously to

enantiomer in Watthey, et al., J. Med. Chem. 1985, 28, 1511-1516). HPLC/MS $[M+H]^+$, 412.

Example 29

5

1-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-2,3-dihydro-1,5-benzthiazepin-4(5H)-one

The title compound was prepared in two steps according to the Carbodiimide Mediated Amide Bond Formation Procedure followed by the Ester Hydrolysis Procedure from 1-carboethoxymethyl-3-amino-2,3-dihydro-1,5-benzthiazepin-4(5H)-one hydrochloride salt (amine free base prepared in US 4512988). HPLC/MS $[M+H]^+$, 430.

15

Example 30

1-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-2,3-dihydro-1,5-benzthiazepin-4(5H)-one S,S-dioxide

20

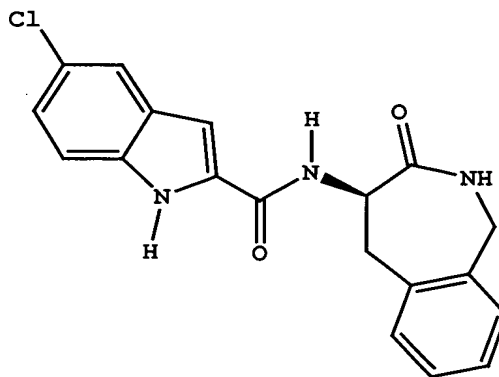
To a solution of 1-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-2,3-dihydro-1,5-benzthiazepin-4(5H)-one (Example 29) (3.7 mg) in dichloromethane (15 mL) at 0°C was added 60% 3-chloroperoxybenzoic acid (5.2 mg gross). After stirring while slowly warming to room temperature over 1 h, water (15 mL) was added. This mixture was stirred for 30 min, the layers were separated, and the organic phase was washed sequentially with 10% aqueous sodium bisulfite solution, 1.0 M aqueous sodium hydroxide solution (10 mL), and brine (10 mL). After drying over anhydrous sodium sulfate, the solvent was evaporated under vacuum, and the residue was purified by reverse phase preparative HPLC to obtain the title compound (2.7 mg). HPLC/MS $[M+H]^+$, 462.

30

Example 31

5 (S)-1-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-
 2,3-dihydro-1,5-benzoxazepin-4(5H)-one

The title compound was prepared in two steps according to the Carbodiimide Mediated Amide Bond Formation Procedure followed by the Ester Hydrolysis
 10 Procedure from (S)-1-carboethoxymethyl-3-amino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride salt (amine hydrochloride salt prepared in US 5552397).
 HPLC/MS [M+H]⁺, 414.

Example 32

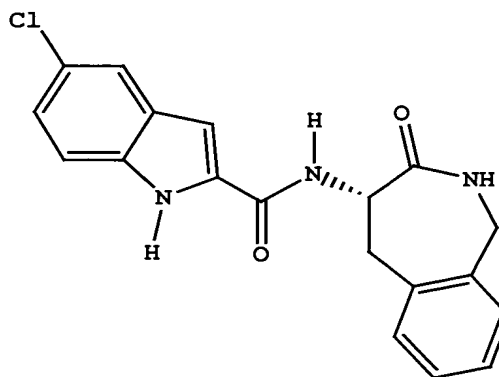
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Example 32

20 (R)-4-(5-chloroindole-2-carbonylamino)-2,3,4,5-
 tetrahydro-2-benzazepin-3(1H)-one

(R)-4-amino-2,3,4,5-tetrahydro-2-benzazepin-3(1H)-one hydrochloride salt (387 mg) (amine free base prepared in US 5545735) was added to a mixture of tetrahydrofuran (40 mL), 5-chloroindole-2-carboxylic acid (356 mg), 1-
 25 hydroxy-7-azabenzotriazole (272 mg), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (382 mg) at room temperature. Diisopropylethylamine (202

mg) was added, and the resulting yellow suspension was stirred under argon for 16 h, during which a solution formed. The solution was evaporated under vacuum and the residue was redissolved in ethyl acetate (100 mL). This
 5 was washed sequentially with 1.0 M aqueous hydrochloric acid (50 mL), 1.0 M aqueous sodium hydroxide (50 mL), water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum. The resulting solid crude product was triturated with 20%
 10 methanol in diethyl ether (20 mL four times). Drying under vacuum provided pure title compound (283 mg).
 HPLC/MS $[M+H]^+$, 354.

Example 33

15

Example 33

(S)-4-(5-chloroindole-2-carbonylamino)-2,3,4,5-
tetrahydro-2-benzazepin-3(1H)-one

20

To a solution of (S)-L-(2-cyanophenyl)alanine (1.0 g) in acetonitrile (30 mL) at room temperature was added di-t-butyl dicarbonate (1.7 g), followed by saturated aqueous sodium carbonate (20 mL, slowly). After stirring
 25 for 16 h, the acetonitrile was removed under vacuum, and the aqueous layer was extracted with ethyl acetate (50 mL three times). The combined organic layers were washed

sequentially with 0.5 M aqueous hydrochloric acid (50 mL) and brine (50 mL) before drying over anhydrous sodium sulfate and evaporation under vacuum to provide (S)-N-t-butyloxycarbonyl(2-cyanophenyl)alanine (1.4 g).

- 5 A mixture of (S)-N-t-butyloxycarbonyl(2-cyanophenyl)alanine (1.0 g), Raney[®] Nickel (1.0 g), and methanol (20 mL) was hydrogenated in a Parr apparatus at 50 psi for 60 h at room temperature. The catalyst was filtered and rinsed with methanol (20 mL three times).
- 10 The combined filtrate and rinses were evaporated under vacuum, and the resulting residue was triturated with diethyl ether (30 mL five times) to obtain (S)-N-t-butyloxycarbonyl(2-aminomethylphenyl)alanine (406 mg).

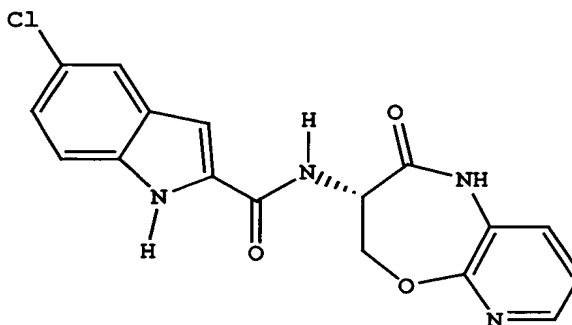
- A mixture of (S)-N-t-butyloxycarbonyl(2-aminomethylphenyl)alanine (353 mg), N,N-dimethylformamide (10 mL), dichloromethane (50 mL), 1-hydroxy-7-azabenzotriazole (252 mg), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (180 mg) was stirred at room temperature for 1 h. The
- 20 solvent was removed under vacuum and the residue was dissolved ethyl acetate (100 mL). This solution was washed sequentially with 1.0 M aqueous hydrochloric acid (50 mL twice), 1.0 M aqueous sodium hydroxide (50 mL), water (50 mL), and brine (50 mL), dried over anhydrous
- 25 sodium sulfate, and evaporated under vacuum to obtain (S)-4-(t-butyloxycarbonylamino)-2,3,4,5-tetrahydro-2-benzazepin-3(1H)-one (315 mg).

- (S)-4-(t-butyloxycarbonylamino)-2,3,4,5-tetrahydro-2-benzazepin-3(1H)-one (276 mg) was dissolved in 2 M
- 30 hydrogen chloride in diethyl ether solution (25 mL) at room temperature. A precipitate slowly formed. After 16 h stirring the solvent was evaporated under vacuum. The residue was twice taken up in toluene (10 mL) and evaporated to provide (S)-4-amino-2,3,4,5-tetrahydro-2-

benzazepin-3(1H)-one hydrochloride, which was used directly in the next step.

A mixture of (S)-4-amino-2,3,4,5-tetrahydro-2-benzazepin-3(1H)-one hydrochloride (all of that prepared
5 above), tetrahydrofuran (25 mL), 5-chloroindole-2-carboxylic acid (198 mg), 1-hydroxy-7-azabenzotriazole (150 mg), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (210 mg) was stirred at room temperature. Diisopropylethylamine (202 mg) was
10 added, and after 16 h the resulting yellow solution was evaporated under vacuum. The residue was dissolved in ethyl acetate (150 mL), and this was washed sequentially with 1.0 M aqueous hydrochloric acid (50 mL twice), 1.0 M aqueous sodium hydroxide (50 mL), water (50 mL), and
15 brine (25 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum to provide crude product. The product was crystallized by dissolving in warm methanol (40 mL) and adding diethyl ether (100 mL). The crystals were filtered, washed with diethyl ether (30 mL twice),
20 and dried under vacuum to provide the title compound (181 mg). HPLC/MS $[M+H]^+$, 354.

Example 34



Example 34

(S)-9-aza-3-(5-chloroindole-2-carboxylamino)-2,3-dihydro-
1,5-benzoxazepin-4(5H)-one

5

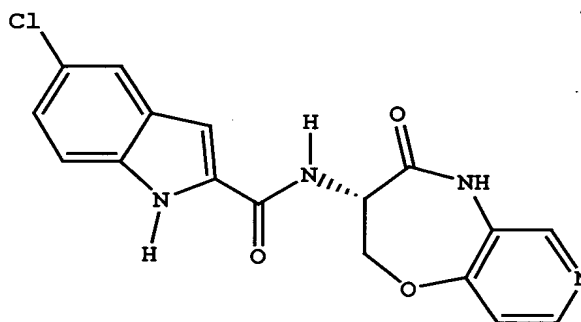
To a stirring solution of N-t-butyloxycarbonyl-L-serine (2.26 g) in N,N-dimethylformamide (15 mL) under argon at -20°C was slowly added sodium hydride (60% oil dispersion, 0.88 g gross weight). The resulting mixture was warmed to 0°C for 1 h, then recooled to -20°C before a solution of 2-chloro-3-nitropyridine (1.6 g) in N,N-dimethylformamide (10 mL) was added over 10 min. The resulting red solution was stirred at -20°C for 1 h. Water (100 mL) was then added, and the mixture was washed with diethyl ether (30 mL twice). The aqueous layer was adjusted to pH 7 with 1.0 M aqueous hydrochloric acid and extracted with ethyl acetate (30 mL three times). The combined extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum. The resulting residue was purified by silica gel chromatography eluting with ethyl acetate - hexane (1:2) to obtain N-t-butyloxycarbonyl-O-(3-nitro-2-pyridyl)-L-serine (2.46 g).

A mixture of N-t-butyloxycarbonyl-O-(3-nitro-2-pyridyl)-L-serine (500 mg) and 10% palladium on carbon (50 mg) in methanol (30 mL) was hydrogenated under a hydrogen balloon for 6 h. The catalyst was filtered off, rinsing with methanol (15 mL twice). The filtrate was evaporated under vacuum, and the residue was purified by reverse phase preparative HPLC using trifluoroacetic acid containing solvents. The preparative HPLC fractions were partially evaporated at 0°C under vacuum before lyophilization to provide N-t-butyloxycarbonyl-O-(3-amino-2-pyridyl)-L-serine trifluoroacetic acid salt (475 mg).

To a suspension of N-t-butyloxycarbonyl-O-(3-amino-2-pyridyl)-L-serine trifluoroacetic acid salt (473 mg) in tetrahydrofuran (25 mL) stirring at room temperature under argon was added 1-hydroxy-7-azabenzotriazole (188 mg), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (264 mg), and then diisopropylethylamine (297 mg). After 17 h the mixture was evaporated under vacuum and reverse phase preparative HPLC using trifluoroacetic acid containing solvents provided (S)-9-aza-3-t-butyloxycarbonylamino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one trifluoroacetic acid salt (142 mg).

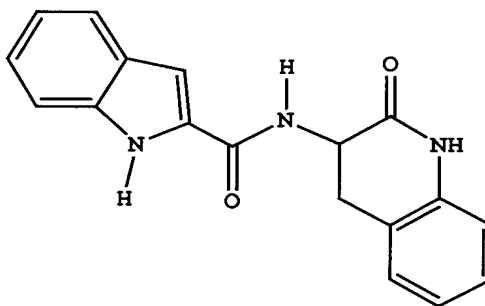
(S)-9-aza-3-t-butyloxycarbonylamino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one trifluoroacetic acid salt (40 mg) was dissolved in dichloromethane (5 mL) and 4 M hydrogen chloride in dioxane solution (2 mL) at room temperature. After 16 h the solvent was evaporated under vacuum, and the residue was twice taken up in toluene (10 mL) and evaporated to provide (S)-9-aza-3-amino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride, all of which was used directly in the next step.

A mixture of (S)-9-aza-3-amino-2,3-dihydro-1,5-benzoxazepin-4(5H)-one hydrochloride, tetrahydrofuran (15 mL), 5-chloroindole-2-carboxylic acid (12 mg), 1-hydroxy-7-azabenzotriazole (8 mg), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (11.5 mg), and diisopropylethylamine (15.5 mg) was stirred at room temperature under argon for 16 h. The solvent was evaporated under vacuum and purification by reverse phase preparative HPLC provided the title compound (18.9 mg). HPLC/MS $[M+H]^+$, 357.

Example 35**Example 35**

- 5 (S)-7-aza-3-(5-chloroindole-2-carbonylamino)-2,3-dihydro-
 1,5-benzoxazepin-4(5H)-one

The title compound was prepared analogously to (S)-
 9-aza-3-(5-chloroindole-2-carbonylamino)-2,3-dihydro-1,5-
 10 benzoxazepin-4(5H)-one (Example 34) using 4-chloro-3-
 nitropyridine in place of 2-chloro-3-nitropyridine. MS
 [M+H]⁺, 357.

Example 36
racemate

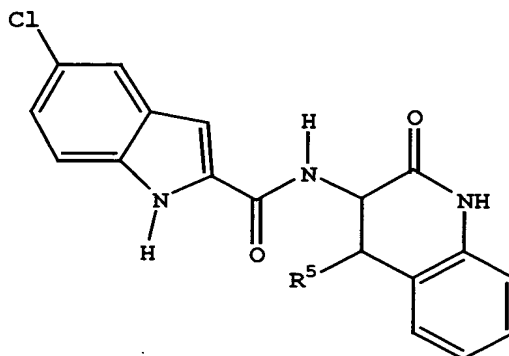
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Example 363-(indole-2-carbonylamino)-3,4-dihydrocarbostyryl

- 20 The title compound was prepared by the methods of
 Example 5 using 3-amino-3,4-dihydrocarbostyryl
 hydrochloride in place of (R)-3-amino-3,4-
 dihydrocarbostyryl hydrochloride and indole-2-carboxylic

acid in place of 5-chloroindole-2-carboxylic acid.
HPLC/MS $[M+H]^+$, 306; $[M+Na]^+$, 328.

Examples 37-41
see table



5

Example	R ⁵	Stereochemistry
37	CH ₂ CO ₂ CH ₃	trans racemate
38	CH ₂ CO ₂ CH ₃	cis racemate
39	CH ₂ CO ₂ H	trans racemate
40	CH ₂ CO ₂ H	trans homochiral enantiomers
41	CH ₂ CONHCH ₂ C ₆ H ₅	cis - trans racemate

Example 37

10 (3R*,4S*)-4-carbomethoxymethyl-3-(5-chloroindole-2-carboxylamino)-3,4-dihydrocarboxtyril (trans racemate)

To a stirred solution of 3-(2-aminophenyl)propenoic acid methyl ester (2.0 g, 11.3 mmol) and triethylamine (3.3 mL, 23.7 mmol) in tetrahydrofuran (36 mL) at room temperature under argon was added 20% w/w phosgene in toluene solution (7 g, 14.1 mmol). After 1 h, a solution of nitromethane (2.9 mL, 54 mmol) in tetrahydrofuran (200 mL) containing 1 M potassium t-butoxide in tetrahydrofuran solution (62 mL, 62 mmol) was added via cannula. The mixture was stirred for 1 h before it was poured into ice-cold 1 M aqueous hydrochloric acid (300 mL). The resulting mixture was extracted with ice-cold diethyl ether (300 mL three times). The combined organic extracts were dried over anhydrous sodium sulfate, and

the solvent was evaporated under vacuum to give crude 3-(2-(nitroacetyl amino)phenyl)propenoic acid methyl ester (1 g, 72% pure) as an orange solid. HPLC/MS $[M+H]^+$, 265.

A 50 mL round-bottom flask was charged with crude 3-(2-(nitroacetyl amino)phenyl)propenoic acid methyl ester (100 mg), methanol (20 mL) and 0.5 M sodium methoxide in methanol solution (2.3 mL). After stirring 18 h at room temperature under argon, with reaction progress monitored by diminution of UV absorbance at 280 nm, the reaction was quenched with glacial acetic acid (5 mL). Raney[®] Nickel (100 mg of 50% w/w water slurry) was added, and the atmosphere evacuated and charged four times with hydrogen gas (1 atm). After the mixture was stirred vigorously for 3 h at room temperature, the vessel was flushed with nitrogen, and the mixture was allowed to settle. The supernatant was decanted, and solvent evaporation under vacuum gave a green solid which was purified by reverse phase preparative HPLC using trifluoroacetic acid containing solvents to obtain 3-amino-4-carbomethoxymethyl-3,4-dihydrocarbostyryl trifluoroacetic acid salt (24 mg, 7% overall yield from 3-(2-aminophenyl)propenoic acid methyl ester) as a white solid. This material was comprised of two fractions, a 3:1 mixture of cis and trans isomers (11 mg) and pure trans isomer (13 mg). Cis isomer: ^1H NMR (CD_3OD , 400 MHz) δ 7.40-7.03 (m, 4H), 4.55 (d, 1H, $J = 4.7$ Hz), 3.9-3.85 (m, 1H), 3.81 (s, 3H), 2.82 (dd, 1H, $J = 4.8, 15.8$ Hz), 2.50 (dd, 1H, $J = 9.6, 15.8$ Hz). Trans isomer: ^1H NMR (CD_3OD , 400 MHz) δ 7.33-7.25 (m, 2H), 7.14-7.00 (m, 1H), 6.98 (d, 1H, $J = 7.9$ Hz), 4.41 (d, 1H, $J = 12.3$ Hz), 3.74 (s, 3H), 3.65-3.61 (m, 1H), 3.20 (dd, 1H, $J = 4.3, 17.8$ Hz), 2.95 (dd, 1H, $J = 6.1, 17.6$ Hz).

A 1 mL reaction vessel was charged with trans 3-amino-4-carbomethoxymethyl-3,4-dihydrocarbostyryl

trifluoroacetic acid salt (13 mg, 0.04 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (9 mg, 0.05 mmol), 1-hydroxy-7-azabenzotriazole (7 mg, 0.05 mmol), 5-chloroindole-2-carboxylic acid (8 mg, 0.04 mmol) and N,N-dimethylformamide (0.3 mL). After the solids dissolved during stirring at room temperature under argon, diisopropylethylamine (14 mg, 0.11 mmol) was added, and the solution was stirred for 1 h before it was diluted with water (0.2 mL) and methanol (0.8 mL).

10 Purification by reverse phase preparative HPLC using trifluoroacetic acid containing solvents gave the title compound (8.5 mg, 56% yield) as a white solid. ¹H NMR (d₈-THF, 400 MHz) δ 11.2 (s, 1H), 9.6 (s, 1H), 8.06 (d, 1H, J = 8.9 Hz), 7.64 (d, 1H, J = 1.9 Hz), 7.43 (d, 1H, J = 8.7 Hz), 7.24-6.87 (m, 6H), 4.84 (dd, 1H, J = 8.8, 13.0 Hz), 3.67 (m, 1H), 3.59 (s, 3H), 2.89 (d, 2H, J = 6.2 Hz). HPLC/MS [M+H]⁺, 412.

Example 38

20

(3R*,4R*)-4-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (cis racemate)

Following the procedure for the last step of Example 37, the title compound was prepared from a 3:1 mixture of cis and trans, respectively, 3-amino-4-carbomethoxymethyl-3,4-dihydrocarbostyryl trifluoroacetic acid salt (prepared in Example 37). The title compound of Example 37 was also isolated by reverse phase preparative HPLC, eluting just after the title compound of Example 38. ¹H NMR (CD₃OD, 400 MHz) δ 7.64-6.93 (m, 8H), 5.03 (d, 1H, J = 5.7 Hz), 3.93-3.91 (m, 1H), 3.50 (s, 3H), 2.73 (dd, 1H, J = 5.2, 15.3 Hz), 2.36 (dd, 1H, J = 9.5, 15.2 Hz). HPLC/MS [M+H]⁺, 412.

Example 39

5 (3R*,4S*)-4-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (trans racemate)

A 250 mL round-bottom flask was charged with 3-(2-aminophenyl)propenoic acid methyl ester (600 mg, 3.39 mmol) and THF (100 mL), and the resulting solution was
10 cooled to 0 °C. To this was added dicyclohexylcarbodiimide (880 mg, 4.26 mmol) and of nitroacetic acid (prepared according to Huang, et al., J. Org. Chem. 2000, 65, 499-503) (430 mg, 4.0 mmol). The reaction solution was stirred for 2 h at 0 °C (solids
15 formed) before warming to room temperature and filtration. The filtrate was evaporated under vacuum to obtain crude 3-(2-(nitroacetylamino)phenyl)propenonic acid methyl ester (1.0 g, 82.5% pure) as a tan solid.

A 500 mL round-bottom flask was charged with crude
20 3-(2-(nitroacetylamino)phenyl)propenonic acid methyl ester (1.0 g), methanol (190 mL), and after degassing by argon sparge for 30 min, 0.5 M sodium methoxide in methanol solution (23 mL). After stirring 5 h at room temperature under argon, with reaction progress monitored
25 by diminution of UV absorbance at 280 nm, the reaction mixture was cooled to -30 °C and 2 M hydrogen chloride in ether solution (7 mL) was added slowly. After partial solvent evaporation to 30 mL at 0 °C under vacuum, the resulting solution was transferred to a 100 mL round-
30 bottom flask containing dry Raney® Nickel (400 mg, prepared from 50% w/w water slurry by repetitive rinsing with methanol (5 mL three times) and solvent evaporation under vacuum). The resulting mixture was stirred vigorously for 14 h at room temperature under hydrogen (1

atm) before it was transferred to a pressure bottle to continue hydrogenation at 40 psi for 2 h. The supernatant was decanted and evaporated under vacuum. The residue was taken up in a mixture of water (200 mL) and diethyl ether (100 mL). After separation of the aqueous layer, the organic layer (containing suspended solids) was diluted with ethyl acetate (50 mL) and extracted with water (100 mL). The combined aqueous extracts were evaporated under vacuum to dryness to obtain crude 3-amino-4-carbomethoxymethyl-3,4-dihydrocarbostyryl hydrochloride (1.2 g).

Crude 3-amino-4-carbomethoxymethyl-3,4-dihydrocarbostyryl hydrochloride (1.2 g) was slurried in N,N-dimethylformamide (11 mL) with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (340 mg), 1-hydroxy-7-azabenzotriazole (240 mg), 5-chloroindole-2-carboxylic acid (300 mg) and diisopropylethylamine (525 mg, added last). The reaction mixture was stirred for 14 h at room temperature before dilution with ethyl acetate (200 mL) and 1.0 M aqueous hydrochloric acid solution (100 mL). After separation of the organic layer, the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed sequentially with 1.0 M aqueous hydrochloric acid solution (100 mL three times), 1.0 M aqueous sodium hydroxide solution (100 mL twice), and brine (100 mL), before drying over anhydrous magnesium sulfate and evaporation under vacuum to obtain crude cis-trans racemic 4-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (360 mg, 26% overall yield from 3-(2-aminophenyl)propenoic acid methyl ester) as a tan solid.

Crude cis-trans racemic 4-carbomethoxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (360 mg, 0.87 mmol) was dissolved in tetrahydrofuran (6 mL)

with lithium hydroxide monohydrate (73 mg, 1.74 mmol) and water (2 mL). After 1 h, 1.0 M aqueous hydrochloric acid solution (1.8 ml) was added and the mixture was evaporated under vacuum to dryness. Epimerization under these hydrolysis conditions produced a 2:1 cis to trans ratio of products. Purification by reverse phase preparative HPLC using trifluoroacetic acid containing solvents gave the title compound (80 mg, 23% yield) as a tan solid. The cis isomer of the title compound was also isolated.

Example 40

(3R*,4S*)-4-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (trans homochiral isomers)

Separation of (3R*,4S*)-4-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl (trans racemate), the title compound of Example 39, into its component enantiomers was accomplished by chiral normal phase preparative HPLC (Chiralcel OD column, elution solvent: methanol containing 0.05% trifluoroacetic acid). High resolution MS calculated for [M-H]⁻, 396.0751.

First isomer to elute: high resolution MS [M-H]⁻ found 396.0770. α_D (21.5°C) = +154.8 (c = 0.50, methanol).

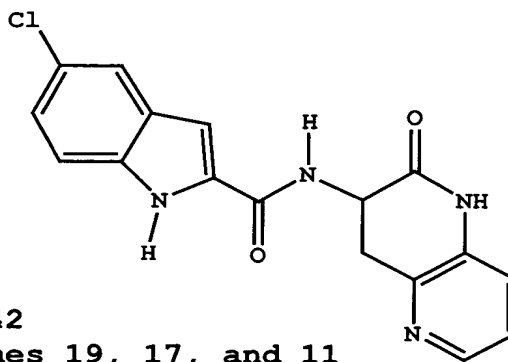
Second isomer to elute: high resolution MS [M-H]⁻ found 396.0770. α_D (21.5°C) = -127.0 (c = 0.50, methanol).

Example 41

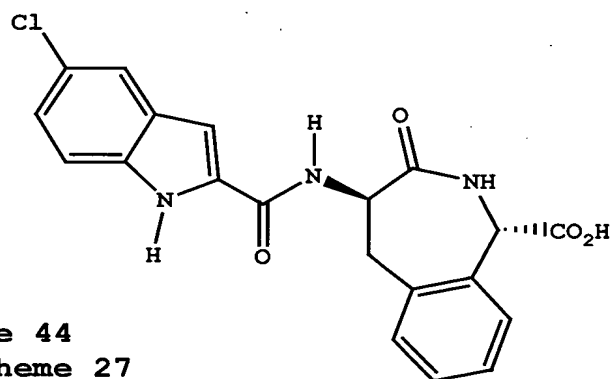
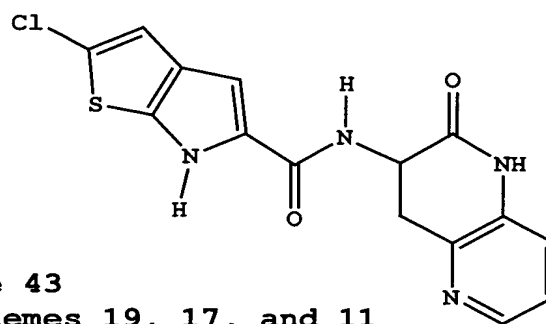
4-benzylaminocarbonylmethyl-3-(5-chloroindole-2-
carbonylamino)-3,4-dihydrocarbostyryl
 (cis-trans racemate)

To a 1 dram vial was added 4-carboxymethyl-3-(5-chloroindole-2-carbonylamino)-3,4-dihydrocarbostyryl as a 2:1 cis-trans racemate (mixture of the Example 39 title compound and its cis isomer, see Example 39) (9 mg, 0.02 mmol), N,N-dimethylformamide (0.2 mL), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (5 mg, 0.02 mmol), and benzylamine (0.01 mL, 0.05 mmol). After the solution was stirred for 14 h, additional 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (10 mg) and benzylamine (0.015 mL) were added. The solution was stirred for 24 h more before dilution with 75% methanol in water (1.3 mL) and direct injection to reverse phase preparative HPLC, which provided the title compound (3.5 mg) as a white solid. HPLC/MS [M+H]⁺, 487; [M-H]⁻, 485.

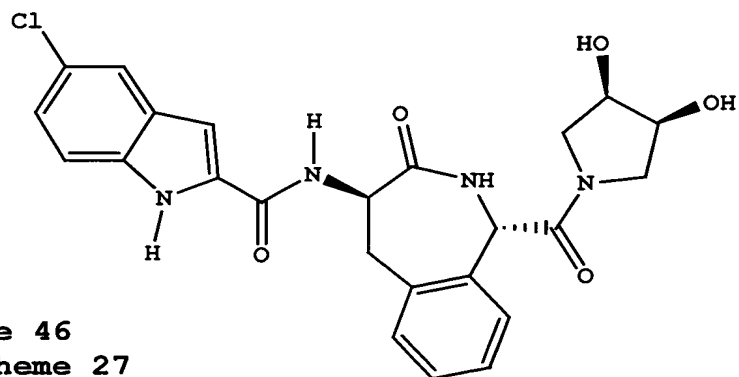
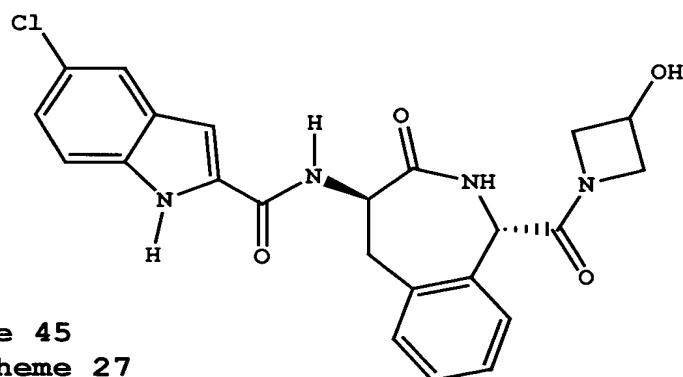
Examples 42 through 55 can be prepared by one skilled in the art using the schemes and prior examples contained herein. These examples serve to further illustrate, but not limit, the scope of the present invention.



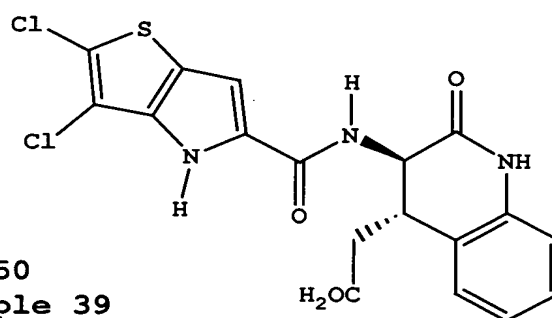
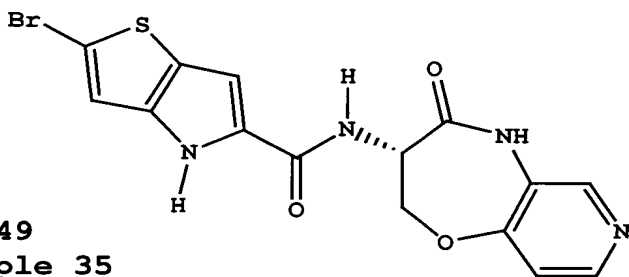
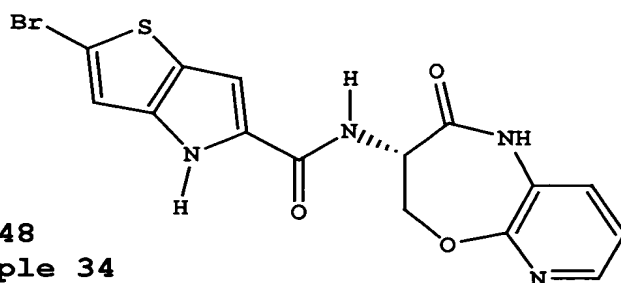
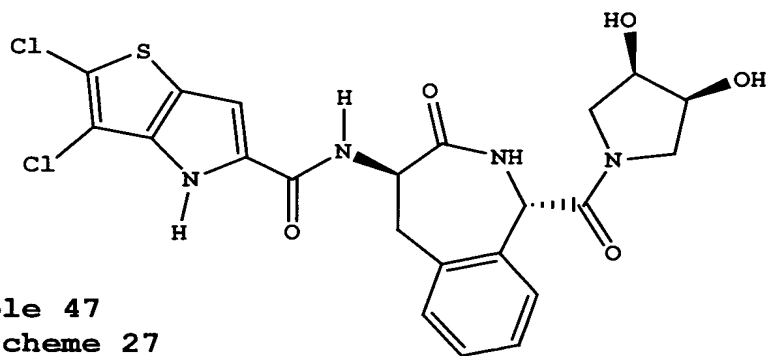
Example 42
 use Schemes 19, 17, and 11

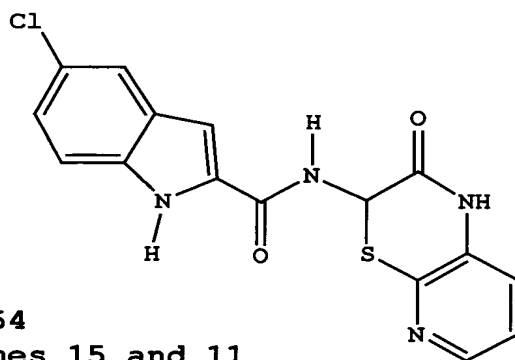
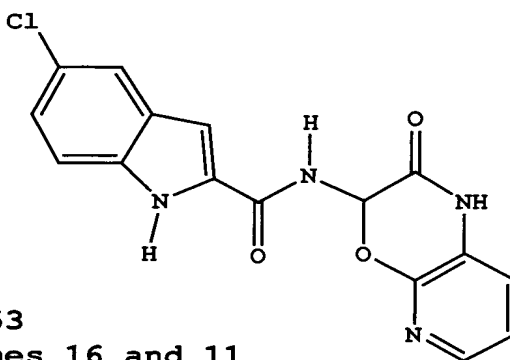
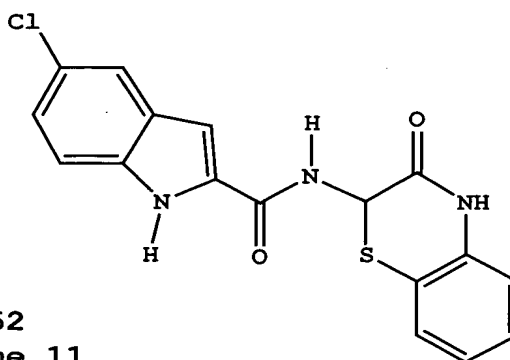
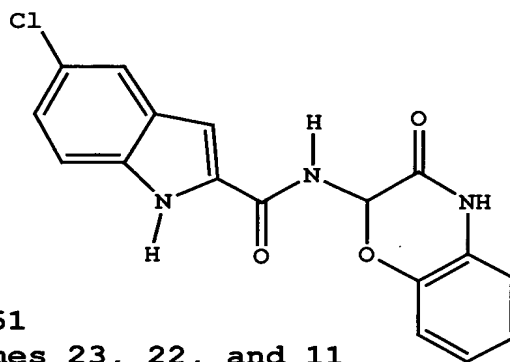


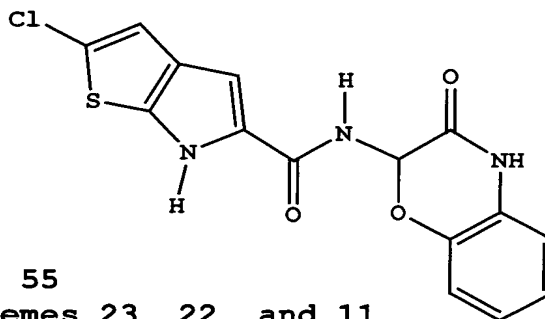
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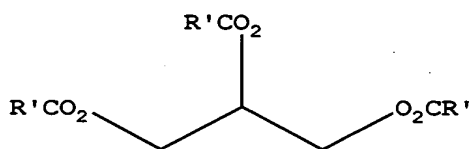
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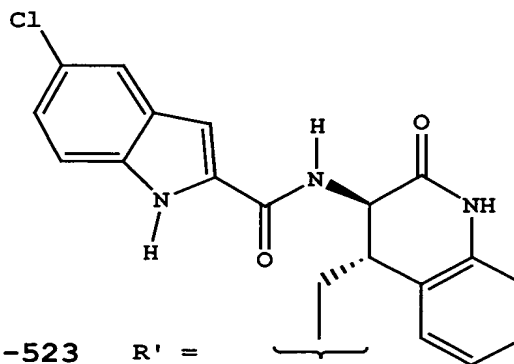




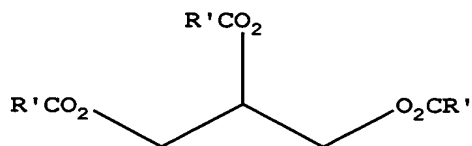
Example 55
use Schemes 23, 22, and 11



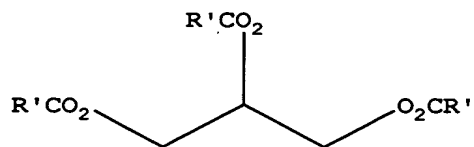
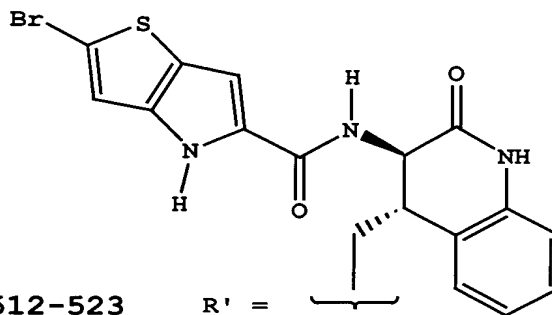
Example 56
see Example 39 and
Bebernitz, et al.,
J. Med. Chem. 2001, 44, 512-523 R' =



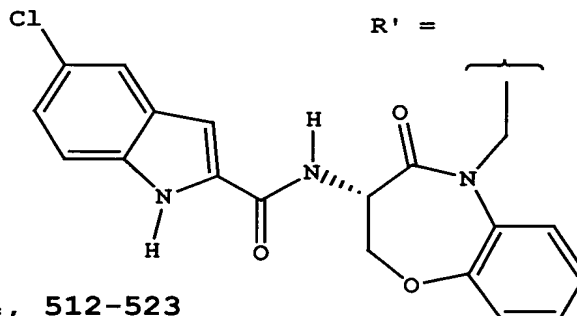
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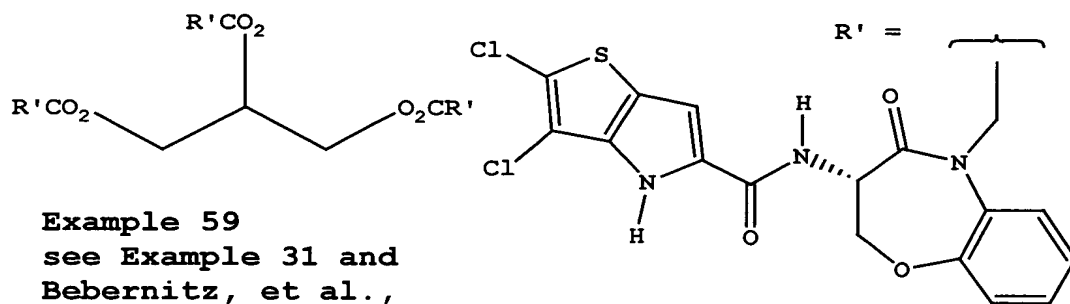
Example 57
see Example 39 and
Bebernitz, et al.,
J. Med. Chem. 2001, 44, 512-523 R' =



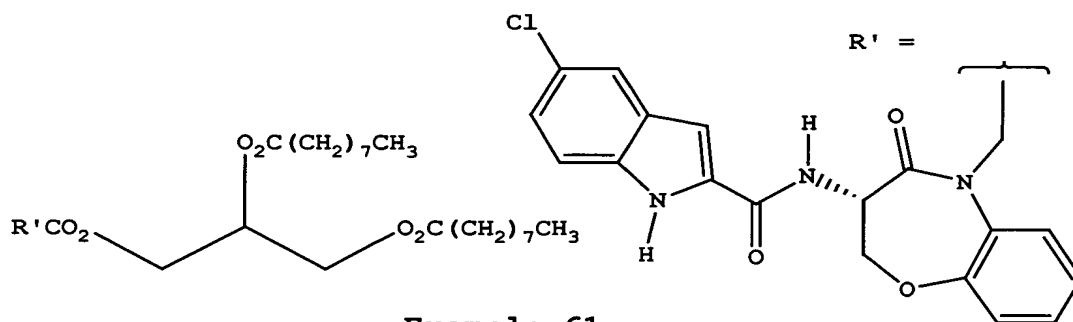
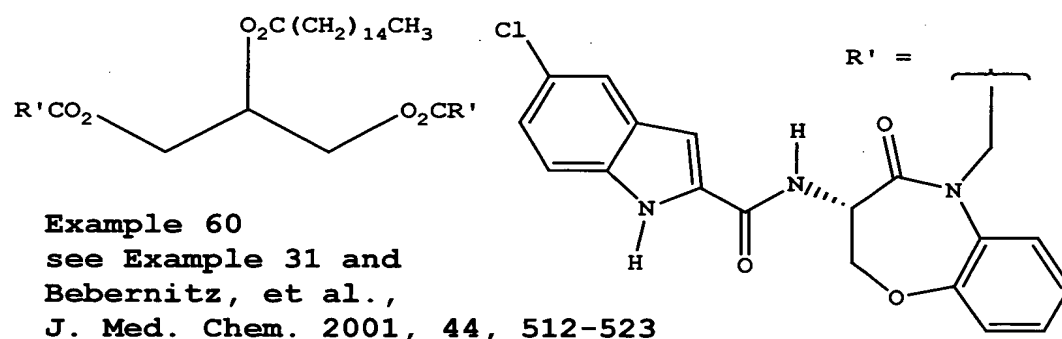
Example 58
see Example 31 and
Bebernitz, et al.,
J. Med. Chem. 2001, 44, 512-523



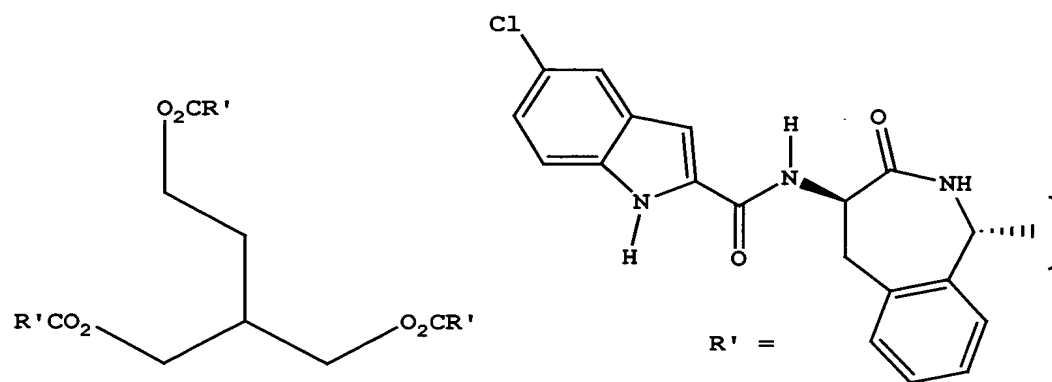
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5



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Example 62
see Example 44 and
Bebernitz, et al.,
J. Med. Chem. 2001, 44, 512-523